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## **Antihypertensive withdrawal for the prevention of cognitive decline (Review)**

Jongstra S, Harrison JK, Quinn TJ, Richard E

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# Antihypertensive withdrawal for the prevention of cognitive decline

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## ABSTRACT

### Background

Clinical trials and observational data have variously shown a protective, harmful or neutral effect of antihypertensives on cognitive function. In theory, withdrawal of antihypertensives could improve cerebral perfusion and reduce or delay cognitive decline. However, it is also plausible that withdrawal of antihypertensives may have a detrimental effect on cognition through increased incidence of stroke or other vascular events.

### Objectives

To assess the effects of complete withdrawal of at least one antihypertensive medication on incidence of dementia, cognitive function, blood pressure and other safety outcomes in cognitively intact and cognitive impaired adults.

### Search methods

We searched ALOIS, the specialised register of the Cochrane Dementia and Cognitive Improvement Group, with additional searches conducted in MEDLINE, Embase, PsycINFO, CINAHL, LILACS, Web of Science Core Collection, ClinicalTrials.gov and the World Health Organization Portal/ICTRP on 12 December 2015. There were no language or date restrictions applied to the electronic searches, and no methodological filters were used to restrict the search.

### Selection criteria

We included randomised controlled trials (RCTs) and controlled clinical trials (CCTs) provided they compared withdrawal of antihypertensive medications with continuation of the medications and included an outcome measure assessing cognitive function or a clinical diagnosis of dementia. We included studies with healthy participants, but we also included studies with participants with all grades of severity of existing dementia or cognitive impairment.

### Data collection and analysis

Two review authors examined titles and abstracts of citations identified by the search for eligibility, retrieving full texts where needed to identify studies for inclusion, with any disagreement resolved by involvement of a third author. Data were extracted independently on primary and secondary outcomes. We used standard methodological procedures expected by Cochrane.

The primary outcome measures of interest were changes in global and specific cognitive function and incidence of dementia; secondary outcomes included change in systolic and diastolic blood pressure, mortality, adverse events (including cardiovascular events, hospitalisation and falls) and adherence to withdrawal. The quality of the evidence was evaluated using the GRADE approach.

### **Main results**

We included two RCTs investigating withdrawal of antihypertensives in 2490 participants. There was substantial clinical heterogeneity between the included studies, therefore we did not combine data for our primary outcome. Overall, the quality of included studies was high and the risk of bias was low. Neither study investigated incident dementia.

One study assessed withholding previously prescribed antihypertensive drugs for seven days following acute stroke. Cognition was assessed using telephone Mini-Mental State Examination (t-MMSE) and Telephone Interview for Cognitive Status (TICS-M) at 90 days as a secondary outcome. The t-MMSE score was a mean of 1.0 point higher in participants who withdrew antihypertensive medications compared to participants who continued them (95% confidence interval (CI) 0.35 to 1.65; 1784 participants) and the TICS-M was a mean of 2.10 points higher (95% CI 0.69 to 3.51; 1784 participants). However, in both cases the evidence was of very low quality downgraded due to risk of bias, indirectness and evidence from a single study. The other study was community based and included participants with mild cognitive impairment. Drug withdrawal was for 16 weeks. Cognitive performance was assessed using a composite of at least five out of six cognitive tests. There was no evidence of a difference comparing participants who withdrew antihypertensive medications and participants who continued (mean difference 0.02 points, 95% CI -0.19 to 0.21; 351 participants). This evidence was of low quality and was downgraded due to risk of bias and evidence from single study.

In one study, the systolic blood pressure after seven days of withdrawal was 9.5 mmHg higher in the intervention compared to the control group (95% CI 7.43 to 11.57; 2095 participants) and diastolic blood pressure was 5.1 mmHg higher (95% CI 3.86 to 6.34; 2095 participants). This evidence was low quality, downgraded due to indirectness, because the data must be interpreted in the context of the wider study looking at glyceryl trinitrate administration or not, and evidence from a single study. In the other study, systolic blood pressure increased by 7.4 mmHg in the withdrawal group compared to the control group (95% CI 7.08 to 7.72; 356 participants) and diastolic blood pressure increased by 2.6 mmHg (95% CI 2.42 to 2.78; 356 participants). This was moderate quality evidence, downgraded as evidence was from a single study. We combined data for mortality and cardiovascular events. There was no clear evidence that antihypertensive medication withdrawal affected adverse events, although there was a possible trend to increased cardiovascular events in the large post-stroke study (pooled mortality risk ratio 0.88, 95% CI 0.72 to 1.08; 2485 participants; and cardiovascular events risk ratio 1.29, 95% CI 0.96 to 1.72). Certain prespecified outcomes of interest (falls, hospitalisation) were not reported.

### **Authors' conclusions**

The effects of withdrawing antihypertensive medications on cognition or prevention of dementia are uncertain. There was a signal of a positive effect in one study looking at withdrawal after acute stroke but these results are unlikely to be generalisable to non-stroke settings and were not a primary outcome of the study. Withdrawing antihypertensive drugs was associated with increased blood pressure. It is unlikely to increase mortality at three to four months' follow-up, although there was a signal from one large study looking at withdrawal after stroke that withdrawal was associated an increase in cardiovascular events.

## **PLAIN LANGUAGE SUMMARY**

### **Antihypertensive withdrawal for the prevention of cognitive decline**

#### **Background**

Dementia and cognitive impairment are a global health concern which place a burden on patients and carers, and increase healthcare costs. Therefore, it is important to identify ways to prevent their occurrence. Previous research has suggested that withdrawal (stopping) of blood pressure lowering medicines might increase the blood flow to the brain and therefore prevent problems of memory and thinking in older age. In this review, we included clinical studies comparing the effects on memory and thinking of withdrawal of blood pressure lowering medicines versus continuation of these medicines.

#### **Included studies**

We found two relevant studies with 2490 participants. The two studies differed in a number of ways. One of the studies withdrew medicine for seven days immediately after a stroke, the other withdrew medicine for three months in older adults with early memory problems.

## **Results**

The two studies did not report new cases of dementia, rather they described performance on standardised tests of memory and thinking. The older-adult study did not find a difference between the participants who stopped and participants who continued medicine. The stroke study found better test scores in participants who stopped medicine, but this must be interpreted with caution since this was measured in such a specific patient population. As expected, blood pressure rose in both studies in the groups that stopped their blood pressure lowering medicines, but there was no short-term increase in heart attacks, strokes or death.

## **Conclusion**

At present, there is not enough evidence to prove or disprove effects of stopping blood pressure medicines on memory and thinking.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

| Antihypertensive withdrawal for the prevention of cognitive decline   |   |   |                           |  |  |   |
|---|---|---|---------------------------|--|--|---|
| <b>Patient or population:</b> adults with cognitive impairment/dementia and cognitively intact populations<br><b>Setting:</b> any setting<br><b>Intervention:</b> antihypertensive withdrawal for the prevention of cognitive decline<br><b>Comparison:</b> antihypertensive continuation |   |   |                           |  |  |   |
| Outcomes  | Anticipated absolute effects* (95% CI)                      |   | Relative effect (95% CI)  | No of participants (studies)                               | Quality of the evidence (GRADE)          | Comments  |
|   | Risk with antihypertensive continuation                     | Risk with antihypertensive withdrawal   |                           |  |  |   |
| Incident dementia - not measured  | n/a   | n/a   | Not estimable             | -  | -  | -   |
| Cognition (at 90 days): t-MMSE score <sup>1</sup>   | The mean t-MMSE score was 9                                 | The mean t-MMSE score in the intervention group was 1 point higher (0.35 to 1.65 points higher)                           | -                         | 1784 <sup>2</sup><br>(1 RCT)<br><a href="#">Bath 2015</a>  | ⊕○○○<br><b>very low</b> <sup>3,4,5</sup> | Lower scores indicate worse cognitive functioning. Participants with acute stroke after 7 days of antihypertensive withdrawal |
| Composite cognitive function <sup>6</sup> (change over 16 weeks)  | The mean change in cognitive function was 0.01 points lower | The mean change in cognitive function in the intervention group was 0.02 points higher (0.19 lower to 0.23 points higher) | -                         | 351 <sup>7</sup><br>(1 RCT)<br><a href="#">Moonen 2015</a> | ⊕⊕○○<br><b>low</b> <sup>3,5</sup>        | Lower total scores indicate worse cognitive functioning. Participants with MCI  |
| Mortality (at 3 to 4 months' follow-up)   | Study population  |   | RR 0.88<br>(0.72 to 1.08) | 2485<br>(2 RCTs)   | ⊕⊕⊕○<br><b>moderate</b> <sup>4</sup>     | -   |
|   | 118 per 1000  | 104 per 1000<br>(85 to 128)   |                           |  |  |   |

|  |                  |                             |                           |   |                                   |   |
|--|------------------|-----------------------------|---------------------------|---|-----------------------------------|---|
| Cardiovascular events<br>(at 3 to 4 months' follow-up) | Study population |                             | RR 1.29<br>(0.96 to 1.72) | 2485<br>(2 RCTs)                              | ⊕⊕○○<br><b>low</b> <sup>4,8</sup> | - |
|  | 61 per 1000      | 79 per 1000<br>(59 to 105)  |                           |   |                                   |   |
| Falls - not measured                                   | n/a              | n/a                         | Not estimable             | -   | -                                 | - |
| Hospitalisations (at 4 months' follow-up)              | Study population |                             | RR 0.85<br>(0.36 to 2.06) | 388<br>(1 RCT)<br><a href="#">Moonen 2015</a> | ⊕⊕○○<br><b>low</b> <sup>5,8</sup> | - |
|  | 53 per 1,000     | 45 per 1,000<br>(19 to 109) |                           |   |                                   |   |

\* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **MCI:** mild cognitive impairment; **n/a:** not available; **RR:** risk ratio; **t-MMSE:** telephone Mini-Mental State Examination.

#### GRADE Working Group grades of evidence

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>1</sup>Telephone Mini-Mental State Examination Score range 0 to 22 points.

<sup>2</sup>Based on number alive at 90 days; data not available by group on number assessed.

<sup>3</sup>Downgraded due to risk of performance bias arising from participants and personnel not being blinded.

<sup>4</sup>Downgraded due to indirectness as majority of study participants were people with acute stroke.

<sup>5</sup>Downgraded as evidence from single study.

<sup>6</sup>Compound overall cognitive score presented. Included components were: time to complete Trail Making Test parts A and B; Interference score of the abbreviated Stroop Color-Word Test; Immediate and Delayed Recall on the 15-word verbal learning test; Visual Association Test and Letter Digit Substitution Test. Compound scores were computed by converting the raw scores of each test to standardised z scores ((test score - mean)/standard deviation) and calculating the mean z scores across the tests in each compound.

<sup>7</sup>Data missing for three in the intervention and two in the control group.

<sup>8</sup>Downgraded due to imprecision.

## BACKGROUND

Hypertension (blood pressure above a recommended value) is a common clinical condition with a well-established causal role in cardiovascular disease (Lewington 2002). Hypertension is particularly prevalent in older age; more than half of the population over the age of 50 years, and approximately 80% of the population older than 80 years have hypertension (Chow 2013; Cohen 2011). The protective effect of antihypertensive treatment against cardiovascular events and premature mortality is well established (Law 2009; Musini 2009). The evidence to support treatment of hypertension in healthy older adults is robust (Beckett 2012). Evidence for benefit of antihypertensive therapy in frail older adults with comorbidities and geriatric syndromes including cognitive and functional decline is limited, and some data suggest potential for harm, with studies describing association between antihypertensive therapy and higher mortality (Benetos 2015a), and serious injuries arising from falls (Tinetti 2014).

The evidence for antihypertensive therapy in people with cognitive impairment or dementia, and the impact of this treatment on cognition is uncertain, with conflicting results in published data and no meta-analysis possible due to heterogeneity (Beishon 2014). Data have variously shown a protective, harmful or neutral effect of antihypertensives on cognition. One study with almost 5000 older adults, suggested no detrimental effect of antihypertensive treatment on cognitive function in people with existing cognitive problems (Skoog 2005). Two other large studies did not show a reduction of incident dementia in people treated with antihypertensive medications (Di Bari 2001; Peters 2008). However, other work suggested a protective effect of antihypertensive treatment on vascular-induced dementia (Tzourio 2003), while another study reported potential for antihypertensive medication to accelerate cognitive decline (Alrawi 2013).

These seemingly conflicting trial data may be explained by the complex relationship between blood pressure and cognition over the life course. Hypertension in middle-age is a risk factor for incident dementia, driven at least in part by cerebrovascular disease (Norton 2014). However, the association between blood pressure and dementia at an older age is inverse (Kennelly 2009; Qiu 2009). Several years before dementia onset, a decrease in blood pressure can be seen (Skoog 1996), and low blood pressure is associated with cognitive decline in the years after diagnosis (Nilsson 2007), although the direction of causality is unknown. Several mechanisms were proposed to underlie this decrease in blood pressure in the years before the diagnosis of dementia, including autonomic dysregulation as symptom of neurodegeneration (den Abeelen 2014). The arteriosclerotic and age-related changes to cerebral blood flow autoregulation in older people could also result in cerebral hypoperfusion, potentially influencing cognitive functioning (Qiu 2009).

Thus, the evidence base for cognitive benefits of hypertension treatment in midlife is compelling, but the evidence for cognitive

effects of hypertension treatment in older age is less clear. The Cochrane systematic review on hypertension treatment in elderly people showed that adherence to treatment is limited and a considerable proportion of older people discontinue treatment, due to adverse effects, in particular when the level of prescribed treatment increased (Musini 2009). Taking all this into account, there is a concern that antihypertensive medication may have potential for harm in people with cognitive impairment/dementia and it may negatively influence cognitive functioning. There is an associated debate regarding the benefit of withdrawing antihypertensive therapy in older adults, since the risk-benefit ratio of treatment might be different at differing ages and with different classes of antihypertensive medications (Shah 2009).

It would be interesting for patients, carers and policymakers if withdrawal of antihypertensive medications has a positive effect on cognitive functioning, since this might possibly lead to a decrease in dementia incidence and thus major health cost savings. Reducing medication use will also contribute to less healthcare expenditures. Such withdrawal may take place in isolation, or may be part of a wider medication review or deprescribing exercise. Deprescribing is “the process of tapering or stopping drugs, aimed at minimizing polypharmacy and improving patient outcome” and is a growing area with observation and trial evidence (Scott 2015). Older adults (Opondo 2012), care home residents (Stafford 2011), and people with advanced dementia (Tjia 2014) are all populations in whom inappropriate prescribing is thought to be common with scope for improvements through deprescribing or electronic systems for medication review.

The purpose of this systematic review was to summarise all available evidence on cognitive effects of withdrawal of antihypertensive medications and associated benefits and harms in adults (including healthy adults and people with prevalent cognitive decline).

## Description of the condition

We have focused on the implications of antihypertensive medication on cognitive functioning, including cognitive decline and dementia. Cognitive decline is often accompanied by deterioration in emotional control, social behaviour or motivation. The number of people living with cognitive impairment not classified as dementia is probably even higher, but no exact data on this exist. The term ‘mild cognitive impairment’ (MCI) refers to a ‘syndrome defined as cognitive decline greater than expected for an individual’s age and education level but that does not interfere notably with activities of daily life’ (Gauthier 2006). Although rates of conversion from MCI to dementia vary, it is thought that people with MCI are at an increased risk of developing dementia (Bruscoli 2004). The term ‘dementia’ refers to a group of diseases which shares a syndrome that is typically chronic and progressive in nature. The dementia syndrome involves disturbances of multiple higher cor-



tical functions, such as memory, thinking, orientation, perception and behaviour, which are severe enough to affect the ability to perform everyday activities. Although the incidence of dementia is thought to be declining in Western countries (Matthews 2016), the prevalence is increasing due to the ageing world population meaning larger numbers of people are living with dementia (Ferri 2005). Worldwide, 47.5 million people were estimated to be affected in 2015 and it is anticipated that this figure will double by 2030, resulting in high costs and considerable burden to individuals and societies (WHO 2015).

## Description of the intervention

In this review, we identified and appraised randomised controlled trials (RCTs) and controlled clinical trials (CCTs) which evaluated the cognitive consequences of withdrawal of antihypertensive treatment in adults. For this review, we defined 'antihypertensive treatment' as the use of any drug with any blood pressure lowering effect, prescribed for any indication.

Major classes of antihypertensive drugs include thiazide diuretics, beta-blockers, drugs inhibiting the renin-angiotensin system, calcium channel blockers, direct vasodilators, centrally active drugs and others. The different classes of antihypertensive drugs have differential effects on some outcomes, and it is possible that they have differential effects on cognition. Some studies have suggested that especially calcium channel blockers (Yasar 2005) and diuretics (Khachaturian 2006; Qui 2003) may have a protective effect on cognition, but this has not been shown in a RCT.

## How the intervention might work

There are plausible theoretical reasons why withdrawal of antihypertensive therapy may have a beneficial effect on cognition. One of these reasons might be autonomic dysregulation as symptom of neurodegeneration (den Abeelen 2014). Another theory is about arteriosclerotic and age-related changes to cerebral blood flow autoregulation in older adults, resulting in cerebral hypoperfusion (Qiu 2009) and potentially influencing cognitive functioning. Equally, withdrawal of antihypertensive therapy may accelerate cognitive decline through incident stroke or progression of small vessel disease.

Interventions to completely withdraw at least one antihypertensive medication in people with and without cognitive problems may also reduce adverse effects and improve quality of life for the patient and carer. However, they may also cause withdrawal symptoms such as 'rebound' tachycardia with withdrawal of beta-blocker, headache, agitation and nausea (Karachalios 2005). Therefore, we have examined trials which evaluate effects of antihypertensive withdrawal, contributing to the evidence base in this area.

## Why it is important to do this review

Contemporary guidelines for blood pressure management in older adults focused on indications for treatment and choice of treatment. It is possible that withdrawal of antihypertensive medication in certain older-adult populations may have beneficial effects on cognition or rates of incident dementia, or both. A cost saving intervention (drug withdrawal) that impacts on cognition would have important individual and public health implications. Drug withdrawal might also decrease the burden of polypharmacy. This burden is usually accompanied with minor and major adverse events, so withdrawal of drugs may have a positive impact. A synthesis of all relevant data moves us closer to adopting evidence-based interventions, or identifies the evidence gaps that require further original research. In general, studies that address the effect of withdrawal of drugs in adult populations are highly relevant to prevent unnecessary and potentially harmful treatments. It is recognised that the initiation and continuation of inappropriate medications is known to negatively impact on the safety of patients (Anathhanam 2012), thus medication withdrawal has the potential to improve safety, provided it does not come with additional greater risks. Finally, improved understanding of medication withdrawal is of particular interest to patients who should be active participants in any deprescribing process. Exploring and addressing their concerns and understanding is critical in successful withdrawal (Reeve 2013), and improving the evidence base behind recommendations is a key component of this.

## OBJECTIVES

To assess the effects of complete withdrawal of at least one antihypertensive medication on incidence of dementia, cognitive function, blood pressure and other safety outcomes in cognitively intact and cognitive impaired adults.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We selected studies if they met the following criteria: RCTs comparing withdrawal of antihypertensive medications with continuation of the medications. We also included CCTs that meet other inclusion criteria. An outcome measure assessing cognitive function or dementia diagnosis had to be clearly defined.

## Types of participants

Participants were aged 18 years and over. Participants must have been taking the antihypertensive medications for a minimum of one month irrespective of indication.

Participants could reside in any healthcare setting (including acute hospitals, nursing and residential homes, and the community). We included healthy participants and participants with all grades of severity of existing dementia or cognitive impairment.

## Types of interventions

Withdrawal of any medication with blood pressure lowering effects (see list of relevant medications included in [Appendix 1](#)) with no restriction to duration of follow-up.

## Types of outcome measures

### Primary outcomes

- Cognitive impairment or rates of incident dementia in cognitively intact and cognitively impaired adults.
- Cognition in the short-term in adults with or without established cognitive impairment.

Cognitive function quantified with a recognised assessment instrument including multiple cognitive domains, for example (but not limited to) Folstein's Mini Mental State Examination (MMSE) ([Folstein 1975](#)), Montreal Cognitive Assessment (MoCA) ([Nasreddine 2005](#)), more extensive neuropsychological testing, or formal clinical diagnosis of dementia according to current internationally accepted guidelines, for example (but not limited to) International Classification of Diseases and Related Health Problems (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

### Secondary outcomes

- Changes in systolic and diastolic blood pressure.
- Rates of (serious) adverse events across the included studies. These included mortality, cardiovascular events, early (within first eight weeks) and late (post-six months) adverse effects (e.g. falls and hospitalisation).
- Adherence to withdrawal of the antihypertensive medications. We defined adherence to withdrawal as participants remaining off medication for the duration of the study or at least six months, whichever was longer.

## Search methods for identification of studies

We used the electronic databases listed below to search for relevant studies regardless of language, personnel, research setting or date of publication.

## Electronic searches

We searched ALOIS ([www.medicine.ox.ac.uk/alois](http://www.medicine.ox.ac.uk/alois)) - the Cochrane Dementia and Cognitive Improvement Group's (CD-CIG) specialised register on 12 December 2015.

ALOIS is maintained by the Trials Search Co-ordinator for the CDCIG, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy older adult populations. The studies are identified through:

- monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS;
- monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the World Health Organization (WHO) portal (which covers [ClinicalTrials.gov](#); [ISRCTN](#); the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
- quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL); and
- six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses and Australasian Digital Theses.

To view a list of all sources searched for ALOIS see [AboutALOIS](#) on the ALOIS website ([www.medicine.ox.ac.uk/alois](http://www.medicine.ox.ac.uk/alois)).

Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement trials, can be viewed in the 'Methods used in reviews' section within the editorial information about the [Cochrane Dementia and Cognitive Improvement Group](#).

We ran additional searches in MEDLINE, Embase, PsycINFO, CINAHL, LILACS, Web of Science core collection, [ClinicalTrials.gov](#) and the WHO Portal/ICTRP to ensure that the search was as comprehensive and up-to-date as possible. See [Appendix 2](#) for the search strategy that we used to retrieve reports of trials from MEDLINE (via the OvidSP platform).

## Searching other resources

In case of incomplete reports or conference abstracts, we conducted further searches for connected papers and, if necessary, we contacted authors to obtain missing information.

We handsearched the reference lists of the relevant articles that we retrieved and searched for non-MEDLINE listed journals. We also searched the Science Citation Index for articles citing key references. We emailed two North American research groups with active deprescribing research programmes to check we had not missed any relevant studies.

## Data collection and analysis

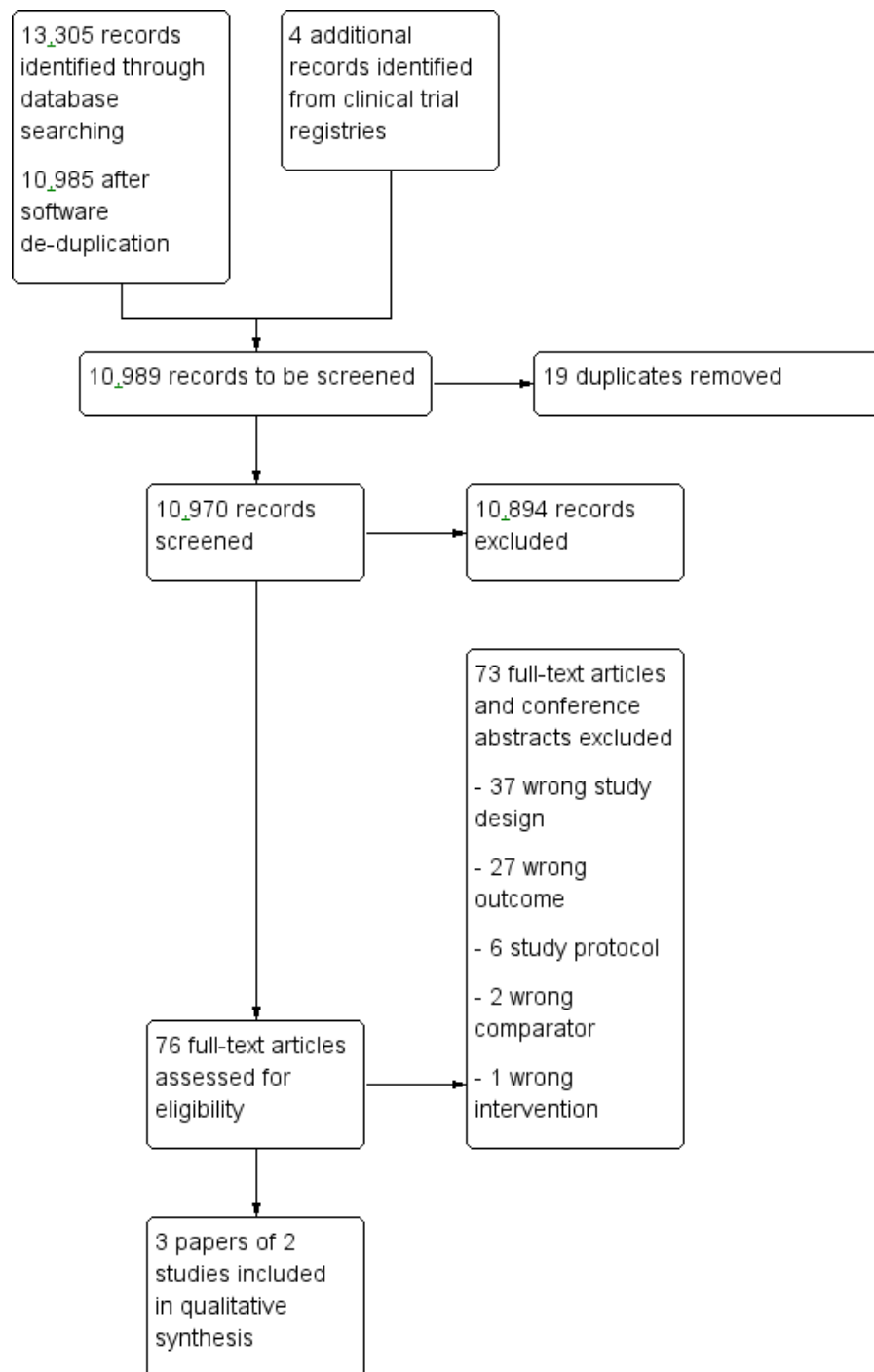
### Selection of studies

Phase 1: two review authors (SJ and JH) independently performed searches and screening of identified studies. We independently examined titles and abstracts of citations obtained from the searches and discarded obviously irrelevant articles. At this stage, we were

overly inclusive; we retrieved for further assessment any article that suggested a relevant study.

Phase 2: from the potentially relevant articles in Phase 1, two review authors (SJ and JH) independently selected studies (based on the full-text format) for inclusion. We resolved disagreement on study inclusion by consensus or third party adjudication (ER). We detailed the study selection process in a PRISMA flow diagram ([Moher 2009](#); [Figure 1](#)).

**Figure 1. PRISMA Study flow diagram.**



### Data extraction and management

Two review authors (SJ and JH) independently performed data extraction using a prespecified data extraction form and entered the data into Review Manager 5 software ([RevMan 2014](#)). In case of discrepancies, we involved a third review author (ER) until we reached consensus.

We created and used a specific data extraction form, including source, methods, participants, interventions, outcomes, results, funding source and declarations of interest according to the *Cochrane Handbook for Systematic Reviews of Interventions* guidance ([Higgins 2011](#)).

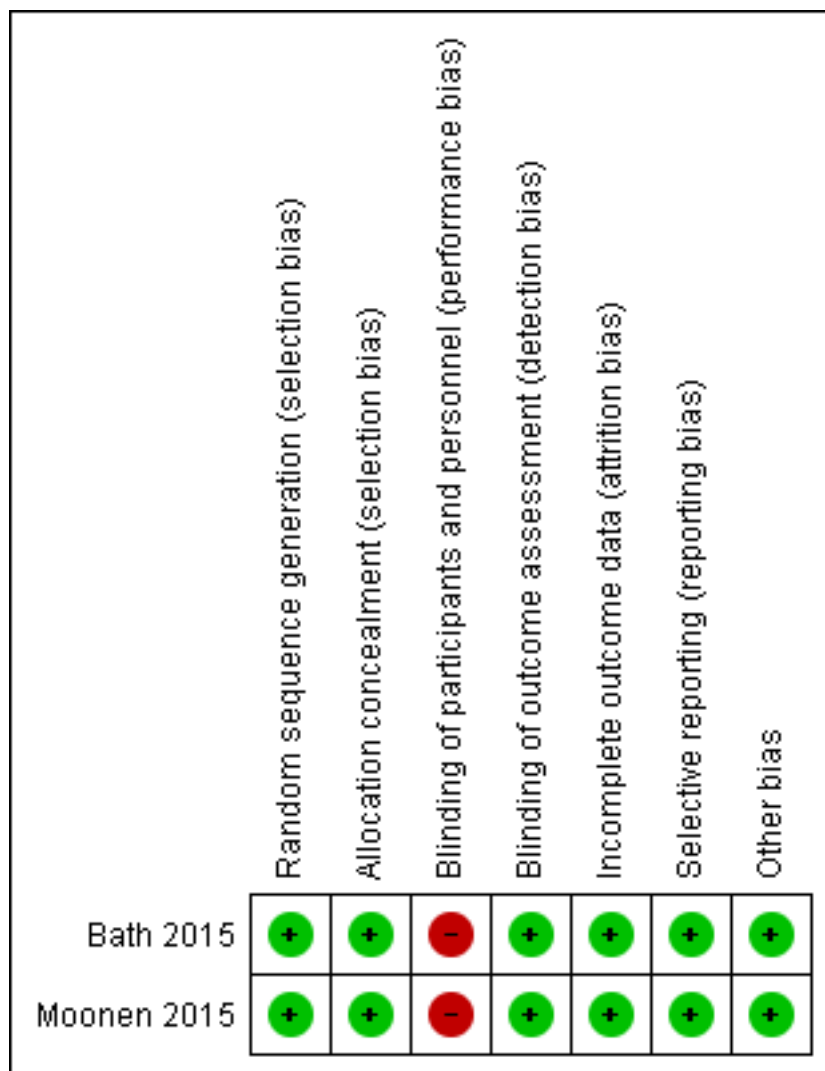
One review author (SJ) entered the data into Review Manager 5, which were checked for accuracy by a second review author (JH)

([RevMan 2014](#)).

### Assessment of risk of bias in included studies

Two review authors (SJ and JH) independently assessed the internal validity of each included study. We described the risk of bias of all included studies in the [Characteristics of included studies](#) table and narrative. We used the Cochrane 'Risk of bias' tool for assessment and we used seven standard criteria: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other risk of bias ([Higgins 2011](#)). We assessed every study for each of the seven criteria and reported the information in a 'Risk of bias' table in [Figure 2](#).

**Figure 2. Cochrane 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**



## Measures of treatment effect

We used mean differences (MD) or standardised mean differences (SMD) with 95% confidence intervals (CI) for continuous outcomes, and risk ratios (RR) with 95% CIs for the analysis of dichotomous outcomes.

Scales that are commonly used in dementia trials are often coded ordinally. We treated the data measured with scales comprising of more than 10 categories as continuous variables assuming a normal distribution.

## Unit of analysis issues

The unit of analysis was the person undergoing the withdrawal of an antihypertensive treatment. As defined in our protocol, we considered for each study whether groups of individuals were randomised together to the same intervention (i.e. cluster-randomised trials), whether individuals underwent more than one intervention (e.g. in a cross-over trial) or whether there were multiple observations for the same outcome (e.g. repeated measurements, recurring events).

### Dealing with missing data

For each outcome measure, we sought data on every participant assessed. To allow an intention-to-treat analysis, we sought the data irrespective of compliance, whether the participant was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. We did not use data from titration phases prior to the randomised phase to assess safety or efficacy. We made a qualitative judgement as to whether to exclude studies if the impact of missing data was too large.

### Assessment of heterogeneity

We considered clinical heterogeneity between trials (participants, interventions and outcomes) when deciding whether to synthesise data. Statistical heterogeneity was considered by using the  $I^2$  test (Higgins 2011). We considered heterogeneity of 30% to 60% as moderate, 50% to 90% as substantial and 75% to 100% as considerable. We made a decision on the appropriateness of meta-analysis based on statistical and clinical heterogeneity.

### Assessment of reporting biases

We searched for non-published as well as published studies in databases and trial registries, to avoid publication bias. To avoid language bias, we did not employ language restrictions for included studies. Where there are multiple publications from one study, we only included the primary publication to address duplicate publication bias.

### Data synthesis

We decided on suitability of meta-analysis for each outcome by a qualitative assessment (including statistical and clinical heterogeneity) of the included studies.

We conducted data synthesis and analyses using Review Manager 5 software (RevMan 2014). We planned to use RRs and a random-effects model to combine outcomes across trials for a meta-analysis. The weighting factor for each study would be the inverse of the within-study variance plus a between-study variance component.

### Subgroup analysis and investigation of heterogeneity

If we had identified 10 or more trials that contributed to the analyses of primary outcomes, we planned to perform stratified analyses of the primary effectiveness outcome according to the following trial characteristics: presence versus absence of dementia or cognitive impairment at baseline, age and type/class of antihypertensive treatment (thiazide diuretics, angiotensin converting enzyme inhibitors (ACE-I), etc.).

### Data presentation - 'Summary of findings' tables

We used the GRADE approach to assess the quality of the supporting evidence behind each estimate of treatment effect (Schünemann 2011a; Schünemann 2011b). We presented key findings of the review including a summary of the amount of data, the magnitude of the effect size and the overall quality of the evidence, in a 'Summary of findings' table, created using GRADEproGDT software (GRADEproGDT 2015). We preselected the following outcomes: cognitive impairment (incident dementia (clinical diagnosis) and change in a validated cognitive test score); change in systolic and diastolic blood pressure; mortality; cardiovascular events; falls; hospitalisation and adherence to withdrawal. Following guidance from the CDCIG editorial team, we decided to exclude change in systolic and diastolic blood pressure and adherence to withdrawal outcomes from presentation in the table.

### Sensitivity analysis

We planned to perform a sensitivity analysis for pooled results based on methodological quality. We also planned to perform sensitivity analyses without CCTs (if identified) to look at the effect of these studies and to avoid risk of bias from the non-randomised design. These sensitivity analyses could not be performed due to the inclusion of only two studies, so there was not enough data to pool.

## RESULTS

### Description of studies

#### Results of the search

The electronic searches performed on 12 December 2015 retrieved 10,989 results. After initial de-duplication two review authors (SJ and JH) independently assessed the remaining 10,970 references for relevance. We received no information for further published or unpublished studies from experts or manufacturers. We excluded 10,894 references that were not relevant on title and abstract screening. Two review authors (SJ and JH) independently assessed 76 full-text articles and conference abstracts for eligibility. Seventy-three articles did not meet our inclusion criteria and were excluded. We included three articles referring to two trials (Bath 2015; Moonen 2015). The selection process is summarised in the PRISMA diagram (Figure 1).

## Included studies

We identified two trials for inclusion with 2490 randomised participants (Bath 2015; Moonen 2015). Bath 2015 is known as the 'Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for the management of high blood pressure in stroke (ENOS) study'. Moonen 2015 is known as the 'Discontinuation of antihypertensive treatment in elderly people on cognitive functioning (DANTE) study'. In addition to the [Characteristics of included studies](#) table, we reported additional information on the included studies in [Table 1](#). We did not contact the authors of either of the included studies since this was not deemed necessary.

## Participants

The ENOS study randomised 4011 participants, although only 2097 participants were included in the antihypertensive withdrawal substudy, as the remainder were not taking antihypertensive medication before admission (Bath 2015). Participants who were included in the antihypertensive withdrawal substudy had a more severe phenotype than those who were not taking antihypertensive drugs before randomisation; they were older, more likely to be women, had higher rates of vascular risk factors and were less likely to have a normal premorbid Rankin Scale score. The DANTE study randomised 393 participants (Moonen 2015).

The populations recruited into the two studies were clinically distinct. In Bath 2015, all participants had to have experienced an acute stroke, while in Moonen 2015, all participants had MCI (defined as an MMSE score between 21 and 27) and taking antihypertensive medications.

The mean age of participants in the DANTE study was 81 years (Moonen 2015), in comparison with 73 years in the ENOS study (Bath 2015). Moonen 2015 only included people aged 75 years and older. Men were 39% to 42% of the study population in DANTE in comparison with 50% to 52% of the study population in ENOS.

Both studies reported comorbidities at baseline and these seemed comparable between intervention and control groups (Bath 2015; Moonen 2015).

Systolic blood pressure was higher at baseline in the ENOS study at 166 mmHg to 168 mmHg (Bath 2015) in comparison to 147 mmHg to 148 mmHg in the DANTE study, whose eligibility criteria limited systolic blood pressure to 160 mmHg (Moonen 2015).

Moonen 2015 assessed cognitive status at baseline and follow-up, while in Bath 2015, cognitive status was unknown at baseline and only evaluated at follow-up. One study excluded people with dementia (Moonen 2015).

Only one study reported level of education at baseline, which was comparable between groups (Moonen 2015).

Both studies included participants taking any classes of antihypertensive treatment. Most participants in both studies were taking more than two antihypertensive medications, more than 60% of

participants in DANTE (Moonen 2015) and more than 50% of participants in ENOS (Bath 2015). Diuretic use was higher in DANTE (54%) than ENOS (16%) and ACE-I use was lower in DANTE (35%) than ENOS (48%).

## Setting

The two clinical settings also varied. Bath 2015 was a large international multicentre study conducted in acute hospital settings, recruiting participants at hospital admission. More than 60% were recruited in the UK, with the remainder worldwide (Bath 2015). Moonen 2015 was conducted in primary care in the Leiden region of the Netherlands, with participants recruited by general practitioners (GPs).

## Interventions and comparators

The interventions reported in each of the studies vary in duration of antihypertensive withdrawal from seven days (Bath 2015) to three months (Moonen 2015).

Bath 2015 was a parallel-group design RCT with four groups. The entire sample was randomised to receive a glyceryl trinitrate (GTN) patch (intervention) or no patch (control). All participants who were taking antihypertensive medications prior to admission (2097/4011 participants) were then additionally randomised to stop their antihypertensive medications (intervention) or to continue pre-existing antihypertensive medications (control). Both the GTN intervention and antihypertensive withdrawal were for the first seven days following an acute stroke admission. Thereafter medications could be prescribed or reintroduced as clinically indicated.

Moonen 2015 was a parallel-group design RCT with two groups. Over an initial six-week period, antihypertensive medications were withdrawn by the participant's GP using a withdrawal algorithm designed by the study authors. This was done provided systolic blood pressure did not exceed 180 mmHg. Medication withdrawal was completed within four weeks from randomisation and continued for a period of three months thereafter.

## Funding sources

The UK Medical Research Council funded Bath 2015 and a grant from the Program Priority Medicines for the Elderly, the Netherlands Organization for Health Research and Development, funded Moonen 2015.

## Excluded studies

We excluded 77 publications, conference abstracts and registered trials and presented the reasons for exclusion in the [Characteristics of excluded studies](#) table. Reasons for study exclusion were: wrong study design (not an RCT or CCT); wrong outcome measure (lack of cognitive outcome measure used); wrong comparator (the



study did not compare participants withdrawing antihypertensive medications with participants continuing them); wrong intervention (participants were not randomised to withdraw or continue antihypertensive medications) and study protocol (planned work without results reported; none met our eligibility criteria for inclusion as ongoing studies).

### Risk of bias in included studies

Overall, the quality of included studies was high (see [Characteristics of included studies](#) table, [Figure 2](#)), with the exception of high risk for performance and attrition bias in both studies.

#### Allocation

Both studies were at low risk of selection bias as they used a central computerised randomisation procedure for allocation of participants. Stratification was used to ensure that the groups were balanced and key parameters appeared adequately divided between intervention and control groups in each study.

#### Blinding

Both studies were at high risk of performance bias as neither masked the participants or medical personnel associated with the study to the treatment allocation. No placebo medications were administered to participants who had usual antihypertensive therapy withdrawn. Since the outcome measurement in each of the two studies was blinded, this minimised the effect of bias on the different outcome measures.

Both studies were at low risk of detection bias as outcome assessment was conducted independently of the study team and assessors were masked to the treatment allocation of the participants.

#### Incomplete outcome data

Overall, the risk of attrition bias was low for both studies because they applied an intention-to-treat analysis. With respect to the primary outcome of this review, cognitive performance, both studies were at high risk for attrition bias. We graded this as high risk for attrition bias according to the [GRADEproGDT 2015](#) guidelines and reported this in [Summary of findings for the main comparison](#). Although both studies presented an intention-to-treat analysis for their results, not all surviving participants received cognitive testing at follow-up and the studies did not report the reasons to account for missing data. [Bath 2015](#) reported cognitive assessment on 1272 (telephone Mini-Mental State Examination (t-MMSE) score) and 1179 (Telephone Interview for Cognitive Status (TICS-M) score), although 1784 survived at 90 days. [Moonen 2015](#) reported the intention-to-treat analysis for 356 participants, while they randomised 388 participants. From those 356 participants,

data were missing for three in the intervention group and two in the control group for their primary outcome (overall cognitive function).

#### Selective reporting

Both studies were at low risk of reporting bias as outcomes were reported as described in the published protocols. The protocol for [Moonen 2015](#) was included in the published paper as a supplemental appendix and the analysis plan for [Bath 2015](#) was published separately ([Bath 2014](#)).

#### Other potential sources of bias

Both studies were at low risk for other potential sources of bias as none were identified.

### Effects of interventions

See: [Summary of findings for the main comparison Antihypertensive withdrawal for the prevention of cognitive decline](#)

See [Summary of findings for the main comparison](#) for an overview of the results.

### Primary outcomes

#### Incident dementia

Neither study evaluated the presence of incident dementia at follow-up.

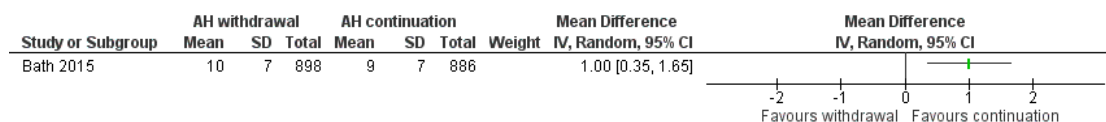
#### Change in cognitive test scores

##### Cognitive function (at 90 days)

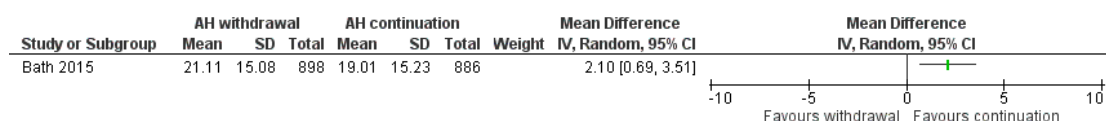
[Bath 2015](#) report data at 90 days for cognitive assessment conducted via the telephone. The numbers assessed in each group were not reported and so the denominator used was the number alive at 90 days. It is recognised this is an overestimate as the number alive at 90 days was 1784, whereas the number who received a t-MMSE was 1272 and the TICS-M was 1179.

The t-MMSE score was a mean of 1.0 point higher in participants who withdrew antihypertensive medications compared to participants who continued them (95% CI 0.35 to 1.65; 1784 participants). The TICS-M was a mean of 2.10 points higher (95% CI 0.69 to 3.51; 1784 participants) ([Figure 3](#); [Figure 4](#)). However, in both cases, the evidence was of very low quality (downgraded due to risk of bias from missing cognitive outcome data, evidence from a single study and indirectness).

**Figure 3. Forest plot of comparison: I Cognitive function (at 90 days), outcome: I.1 Telephone Mini-Mental State Examination score.**



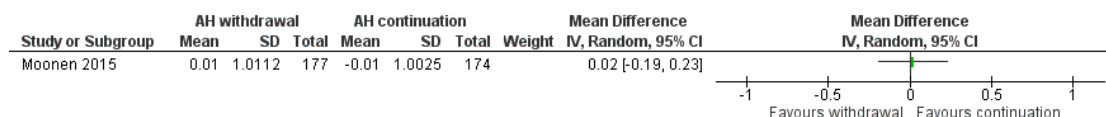
**Figure 4. Forest plot of comparison: I Cognitive function (at 90 days), outcome: I.2 Modified Telephone Interview for Cognitive Status score.**



#### Change in cognitive performance (over 16 weeks)

Moonen 2015 report data for 351/388 participants on their primary outcome of cognitive performance using a composite of at least five out of six cognitive tests. A higher score represented a better cognitive performance. There was no evidence of a mean difference in cognitive performance between participants who withdrew antihypertensive medications than participants who continued (MD 0.02 points, 95% CI -0.19 to 0.23; 351 participants) (Figure 5). This evidence was of low quality (downgraded due to risk of bias from missing cognitive outcome data and evidence from a single study).

**Figure 5. Forest plot of comparison: 2 Change in cognitive function (over 16 weeks), outcome: 2.1 Composite score.**



Each of the six cognitive tests were reported independently for 356/388 randomised participants. There was no evidence of change in cognitive performance in participants who withdrew medications using the MMSE score (MD 0.34 points, 95% CI -0.08 to 0.76; 356 participants); the 15-Word Verbal Learning Immediate Recall score (MD 0.24 points, 95% CI -0.66 to 1.14; 356 participants); the Delayed Recall score (MD 0.16 points, 95% CI -0.29 to 0.61; 356 participants); or the Visual Association Test score (MD 0.14

points, 95% CI -0.17 to 0.45; 356 participants). This evidence was low quality (downgraded due to risk of bias from missing cognitive outcome data and evidence from a single study). There was no evidence of change in cognitive performance in participants who withdrew medications using the Stroop Interference score (MD -2.22 points, 95% CI -9.62 to 5.18; 356 participants) or the Trail Making Tests score (MD 10.06 points, 95% CI -2.20

to 22.32; 356 participants). In both cases, evidence was very low quality (downgraded due to risk of bias from missing cognitive outcome data, imprecision and evidence from a single study).

## Secondary outcomes

### Change in systolic and diastolic blood pressure

#### Blood pressure at seven days

Systolic and diastolic blood pressure was assessed in 2095/2097 participants in [Bath 2015](#), with missing data for the other two participants. After seven days, systolic blood pressure was 9.5 mmHg higher in the intervention compared to the control group (95% CI 7.43 to 11.57; 2095 participants) and diastolic blood pressure was 5.1 mmHg higher (95% CI 3.86 to 6.34; 2095 participants). This evidence was low quality (downgraded due to indirectness from the ability to interpret these data within the wider study looking at GTN administration or not and evidence from a single study).

#### Change in systolic blood pressure (over 16 weeks)

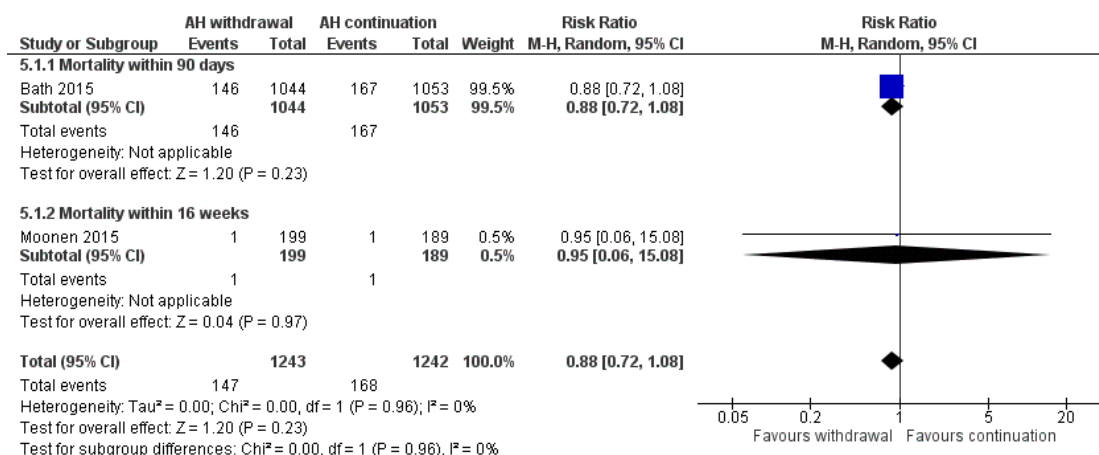
Mean change in systolic and diastolic blood pressure was evaluated for the 356 participants in [Moonen 2015](#). Systolic blood pressure increased by 7.4 mmHg in the withdrawal group compared to the control group (95% CI 7.08 to 7.72; 356 participants) and diastolic blood pressure increased by 2.6 mmHg (95% CI 2.42 to 2.78; 356 participants). This was moderate quality evidence (downgraded due to evidence from a single study).

### Adverse events

#### Mortality

Both studies reported data on mortality at follow-up (16 weeks and 90 days) including all randomised participants for one study ([Bath 2015](#)), and missing data on five randomised participants in the other ([Moonen 2015](#)). There was no evidence that antihypertensive medication withdrawal affected mortality at follow-up (RR 0.88, 95% CI 0.72 to 1.08,  $I^2 = 0\%$ ; 2485 participants; 2 studies; moderate quality evidence (downgraded due to indirectness)) ([Figure 6](#)).

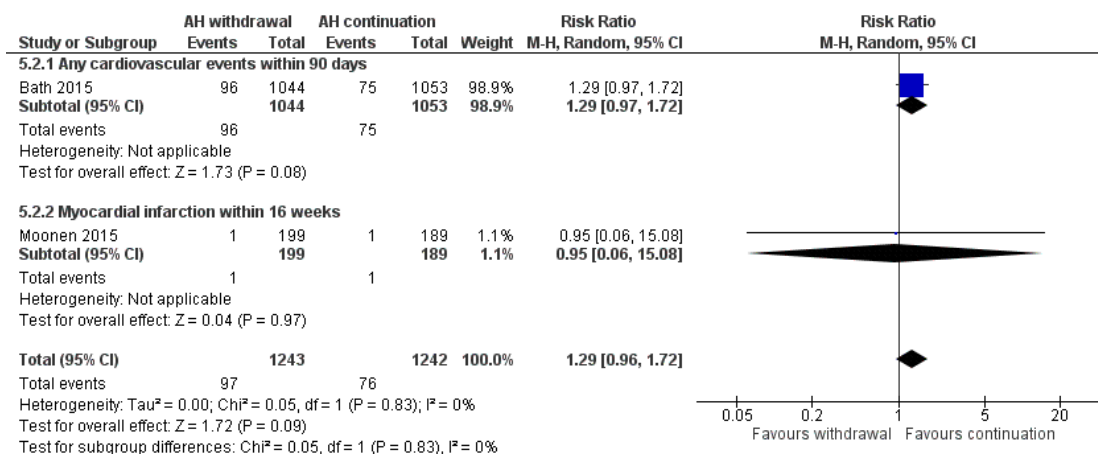
**Figure 6. Forest plot of comparison: 4 Adverse events, outcome: 4.1 Mortality.**



### Cardiovascular events

Both studies reported on cardiovascular events during follow-up. [Moonen 2015](#) reported only myocardial infarction, while [Bath 2015](#) reported myocardial infarction, sudden cardiac death and other cardiovascular events. We pooled the results and there was no evidence of effect of antihypertensive medication withdrawal on the incidence of cardiovascular events (RR 1.29, 95% CI 0.96 to 1.72;  $I^2 = 0\%$ ; 2485 participants; 2 studies; low quality evidence (downgraded due to imprecision and indirectness)) ([Figure 7](#)).

**Figure 7. Forest plot of comparison: 4 Adverse events, outcome: 4.2 Cardiovascular events.**



## Falls

Neither study report data on incidence of falls.

## Hospitalisations

[Moonen 2015](#) reported incident hospitalisations. There was no evidence that antihypertensive withdrawal reduced the risk of incident hospitalisations (RR 0.85, 95% CI 0.36 to 2.06; 388 participants; low quality evidence (downgraded due to imprecision and evidence from a single study)).

## Adherence to withdrawal

[Bath 2015](#) reported adherence to allocated withdrawal or continuation for the entire seven-day period of study. Data were available for 2095/2097 included participants in the continue versus stop arm. A total of 810/1044 participants in the intervention group adhered to stopping antihypertensive therapy compare to 610/1051 participants in the control group adhered to continuation of antihypertensive therapy. Adherence to allocated treatment was higher in participants withdrawing from antihypertensive medication than participants stopping (RR 1.34, 95% CI 1.26 to 1.42; 2095 participants; low quality evidence (downgraded due to indirectness and as results from a single study)).

[Moonen 2015](#) reported no data on adherence to withdrawal of antihypertensive medications.

## Summary of main results

Despite a clear increase in blood pressure in the withdrawal groups of both studies, there was no effect on cognition after seven days or 16 weeks. There was also no effect on cardiovascular events or mortality during the relatively short follow-up in the two studies. The overall quality of the data from the two included studies was high ([Bath 2015](#); [Moonen 2015](#)). However, with respect to our primary outcome measure, cognitive function, we downgraded evidence when applying GRADE methodology ([GRADEproGDT 2015](#)). For both studies, there was a risk of bias introduced from missing cognitive outcomes data and analyses of cognition could not be pooled, meaning data in each case were from a single study. Therefore, we considered the evidence to be low quality for [Moonen 2015](#) and very low quality for [Bath 2015](#) as this was also considered indirect. To put these results in context, it is important to state that our assessment of quality was in relation to our specific study question and is not a statement on the quality of the included trials themselves.

## Dementia and cognitive performance

Neither study evaluated development of incident dementia following medication withdrawal. This lack of evidence for a key question of interest to this review may reflect the short follow-up periods used in both studies (90 days and 16 weeks). This outcome measure is likely to require longer-term surveillance of recruited participants, but would be of particular interest for the DANTE study that included a population considered to have MCI ([Moonen 2015](#)).

The data on cognitive performance is difficult to interpret with

## DISCUSSION

different results depending on the cognitive measure used. Furthermore, determining the clinical significance of the changes observed is key. [Bath 2015](#) contains very low quality evidence of improvement in cognitive performance at 90 days of follow-up; however, we do not know the baseline cognitive function of the included participants and cannot ascertain the effect of the acute event (stroke) and the other intervention studied (nitric oxide) from the effect of antihypertensive withdrawal for a seven-day period. There is also a risk of a survival bias being introduced through the study design, as only participants alive and able to complete cognitive assessment at 90 days were included. Participants who had died or could not be assessed in the telephone assessment were excluded and this reflects the lower numbers in the cognitive analyses. We had to use a proxy denominator in the form of 'alive at 90 days' to incorporate the cognitive data. This overestimates the numbers assessed and reduces confidence in the result presented. [Moonen 2015](#) used a composite cognitive score as their primary outcome and we found low quality evidence that there was no evidence of effect on cognitive performance in participants who withdrew medications over the 16-week study period, compared to participants who continued.

### Blood pressure

We found low quality evidence from one study and moderate quality evidence from the other study that systolic and diastolic blood pressure rise following cessation of antihypertensive medications when compared to participants who continue therapy. This clinically plausible result is consistent; however, it does not appear to be matched with any evidence of increased mortality (moderate quality evidence) or cardiovascular events (low quality evidence). The evidence for treating hypertension in older adults has been established in randomised trials and is known to reduce cardiovascular morbidity and mortality ([Musini 2009](#)).

### Adverse events and safety

A rise in blood pressure may have been anticipated to lead to a rise in adverse events. We found no evidence of a significant increase in cardiovascular events (low quality evidence) or mortality (moderate quality evidence) in either study. We recognise that the studies had a relatively short period of follow-up (months) and that it would take years of follow-up to be certain that the drug withdrawal interventions had no effect on cardiovascular events. Accepting this major caveat, as detailed in our protocol, we pooled data from the available studies for common endpoints of mortality and cardiovascular events. These pooled data suggested no evidence of effect of antihypertensive medication withdrawal on the incidence of cardiovascular events or mortality across the studies, albeit the ENOS study ([Bath 2015](#)) contributes almost all the data.

### Adherence to withdrawal

The results on adherence to withdrawal are difficult to interpret as they could only be extracted from one study ([Bath 2015](#)), and this also evaluated the effects of another medication (GTN) which may lower blood pressure. It is difficult to conclude what effect this had on the adherence of participants allocated to either arm of the study. Data were not reported for participants who recommenced medications in [Moonen 2015](#) despite the inclusion of criteria for re-introduction of medications.

### Overall completeness and applicability of evidence

Only one of the studies identified for inclusion in the review aligned with our study question of interest, namely to examine the cognitive effects of antihypertensive medication withdrawal ([Moonen 2015](#)). Cognition was a secondary outcome measure used by [Bath 2015](#), whose primary question of interest was the safety and efficacy of nitric oxide in the context of acute stroke, with or without continuing existing antihypertensive therapy. This affects the extractable data available and limits the ability to compare the two interventions.

Furthermore, although both populations were at high risk of cognitive decline, the mechanism for these was clinically distinct. [Bath 2015](#) recruited people hospitalised for acute stroke who were recruited into an intervention study of nitric oxide. Here the expected rationale for withdrawing antihypertensive medication would be to maintain or augment blood pressure during an acute (seven-day) period following stroke where it may be plausible to anticipate cerebral perfusion is acutely compromised ([Markus 2004](#)). [Moonen 2015](#) recruited community-dwelling older adults with evidence of reduced cognitive performance where withdrawing medication could be considered to improve cerebral blood flow where brain perfusion may be chronically impaired ([Mossello 2015](#)). Both represent questions of clinical uncertainty and areas of variation in practice.

The procedure for medication withdrawal in [Moonen 2015](#) was described in full in the supplementary material, overseen by the participants' GPs. The procedure used by [Bath 2015](#) was not clearly described. Many participants in the control group also experienced withdrawal of their medication as a consequence of impaired swallow following acute stroke, for part or all of the seven-day period and only 67.8% of participants were adherent for all seven days.

A particular limitation of the data presented is the inability to combine cognitive scores and blood pressure data due to the variations in reporting between the papers. One argument is that the populations were too distinct to pool data. However, if we are to make best use of all available clinical trial data, greater effort must be made in the reporting of outcomes using a more standardised approach. Even if the data had been presented in the same format, we could not have pooled scores as the measures used and the

interventions itself were heterogeneous. This is an area of interest beyond the scope of this review, reflected in international efforts to standardise outcome measure reporting (ICHOM 2016). Additionally, for some of the cognitive outcome measures used in the included studies (t-MMSE in Bath 2015 and cognitive composite score in Moonen 2015), the clinical significance of change in the cognitive test scores is uncertain and this makes a result difficult to interpret on a population level.

Also, neither study focused on the withdrawal of one particular antihypertensive drug (class). Participants were allowed to stop their previously described antihypertensive medications irrespective of the class. We planned to do a subgroup analysis for the different classes of antihypertensives, but due to a lack of data, this could not be done.

Finally, the extent of excluded studies in relation to those eligible for inclusion is important to explore. Two common reasons included the design of the study, principally those identified were observational in design and the lack of use of any cognitive outcome measure at follow-up. The search strategy for this review was comprehensive and designed to incorporate all studies looking at the withdrawal of antihypertensive medications. However, current indexing does not readily identify medication withdrawal studies and this is an additional issue which would benefit from further collaborative work to more easily identify deprescribing studies.

## Quality of the evidence

Data from the two RCTs (2135 participants) could not be pooled for analysis of change in cognitive test score. Evidence was of low quality in relation to cognitive performance. Evidence was downgraded in Moonen 2015 due to risk of bias from incomplete outcome data and assessment of cognitive outcomes and evidence being from a single study. Evidence from Bath 2015 was downgraded to very low quality for the same risk of bias and evidence from a single study plus the indirectness associated with the comparison between blood pressure lowering with GTN and potential interaction with the intervention studied (namely antihypertensive medication withdrawal) as we could not establish who was in the GTN and placebo study arms.

Data from the two RCTs (2135 participants) could not be pooled for analysis of change in blood pressure due to the different reported measures included and clinically distinct periods evaluated. There was low quality evidence of mean systolic and diastolic blood pressure being higher after seven days in participants who stopped antihypertensive medications compared to participants who continued them in Bath 2015, downgraded due to risk of indirectness from the other intervention under study (GTN administration) and evidence from a single study. There was moderate quality evidence of mean rise in both systolic and diastolic blood pressure after 10 weeks of follow-up after antihypertensive medication withdrawal (total study period 16 weeks) in Moonen 2015, downgraded as evidence was from a single study.

On the basis of two RCTs (2485 participants) there was no evidence of effect on mortality or cardiovascular events. However, evidence for mortality was downgraded to moderate quality due to the risk of indirectness associated with the majority of the participants being people with acute stroke compared to community dwellers with MCI. The evidence for cardiovascular events was low quality in view of the same indirectness plus imprecision in the result.

Adherence to withdrawal could only be assessed in one study (2095 participants) and the evidence here was considered low quality, downgraded due to indirectness from the potential use of GTN and the evidence being from a single small study.

No data were available on incidence of dementia or falls.

## Potential biases in the review process

This review has followed Cochrane procedures and there were only minor amendments to the review process from those stated in the protocol, outlined in Differences between protocol and review.

## Agreements and disagreements with other studies or reviews

Cognitive impairment is considered as a significant factor in deprescribing decision-making by geriatricians (Ni Chroinin 2015) and the lack of evidence for people with established dementia needs to be addressed. Much of the developing evidence in this area is not class-specific and is targeted at reducing the overall burden of unnecessary medication use, particularly in the frail older-adult population (Tjia 2013). One limitation of our approach may be the focus on a single drug class, although this benefits from clarity in observing the effect of withdrawal on drug-specific outcome measures.

Antihypertensive medication withdrawal is a topic of interest not only limited to cognitive effects. We await the results of a UK feasibility study of antihypertensive medication withdrawal for people with dementia (van der Wardt 2016).

There are other systematic reviews that have been looking to the protecting effects of antihypertensive medications on cognition (Levi Marpillat 2013; Tully 2016; Zhuang 2016), most of them showing a protective effect of one or more drug classes. Despite these results, it is also important to look at the effect on cognition with drug withdrawal, since this reduces the polypharmacy and is more cost-effective than continuing or introducing drugs.

This review is one of a suite of Cochrane Reviews, looking at withdrawal of specific drug(s) or drug classes in the context of cognition. An additional Cochrane Review, describing antihypertensive withdrawal with a non-cognitive focus is underway and will provide complementary data.



## AUTHORS' CONCLUSIONS

### Implications for practice

It is uncertain whether withdrawal of antihypertensive medications has an influence on cognition or can prevent dementia or cognitive impairment in healthy adults or adults with impaired cognition. Withdrawing antihypertensive drugs was associated with increased blood pressure levels. It is unlikely to increase mortality at three to four months' follow-up, although there was a signal from one large study looking at withdrawal after stroke that withdrawal was associated an increase in cardiovascular events.

### Implications for research

Review of the included and excluded studies suggests possible avenues for future drug withdrawal study design and conduct. For our primary focus of antihypertensives and cognition, further research should include older people and have suitably long follow-up to capture changes in rates of cognitive decline or incident dementia. A classical randomised controlled trial (RCT) design can be used for deprescribing, just as it can for studies of new drugs, although the need for a placebo or an alternative treatment in the withdrawal group is debatable. For studies of withdrawal of a drug class, such as antihypertensives, matched placebos would be almost impossible to achieve for all different kinds of antihypertensive treatment. Ideally, new RCTs looking at withdrawal of antihypertensives (or other drugs) should standardise their cognitive and other outcome measures. There are many ways to measure cognitive function, but these are not always comparable since they may measure different cognitive domains. This heterogeneity

precludes comparisons between studies and complicates meta-analysis.

Deprescribing medications in general is becoming a major subject for new research projects ([deprescribing.org](http://deprescribing.org)). Optimising medication through deprescribing can be a vital part of managing chronic conditions, reducing adverse effects and improving outcomes, including cognitive outcomes. The deprescribing rubric includes many approaches, withdrawal of all but essential drugs; withdrawal of drugs considered to have increased risk in older adults; withdrawal of drug classes and withdrawal of single agents. Each approach is suited to a particular research question. For future studies looking at antihypertensive withdrawal, a focus on one type (class) of drug may be preferable, as cognitive effects may vary with drug class and withdrawal studies which are too broad may miss important class-specific effects. The heterogeneity in approach to drug withdrawal that is included in the umbrella term 'deprescribing' complicates systematic review. To progress the deprescribing agenda, we need agreed descriptive terms for the various approaches. As the literature on deprescribing research increases, it may help future reviews if search filters for this study methodology are developed.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

#### Bath 2015

|               |  |
|---------------|--|
| Methods       | <p>Design: randomised controlled parallel group trial</p> <p>Date of study: 20 July 2001 to 14 October 2013</p> <p>Sample size calculation: yes, needed 1750 for primary outcome</p> <p>Inclusion criteria: adults with a clinical stroke syndrome with limb weakness lasting at least 1 hour (i.e. not likely to be a transient ischaemic attack), residual limb weakness at the time of enrolment, with onset &lt; 48 hours, conscious (Glasgow Coma Scale &gt; 8), systolic blood pressure in range 140 mmHg to 220 mmHg inclusive on the basis of at least 1 of the 3 baseline prandomisation measures, independent prior to stroke (premorbid mRS &lt; 2) and capable of a meaningful consent, or assent from a relative or carer if the person was unable to give meaningful consent (e.g. in cases of dysphasia, confusion or reduced conscious level)</p> <p>Exclusion criteria: a definite need to start (e.g. for thrombolysis), continue or stop blood pressure lowering drugs; need for, or contraindication to, glyceryl trinitrate; coma (Glasgow coma scale score &lt; 8); pure sensory stroke; isolated dysphasia; preceding moderate or severe dependency (mRS score 3 to 5); confounding neurological or psychiatric disease; a disorder mimicking stroke (e.g. hypoglycaemia, Todd's paresis); liver dysfunction (international normalised ratio &gt; 1.5, aminotransferase &gt; 3 times normal concentrations) or renal dysfunction (creatinine &gt; 3 times normal concentrations); severe concomitant medical disorder; pregnancy or breastfeeding; previous participation in the ENOS trial; planned surgical intervention or participation in another trial within 2 weeks</p> |
| Participants  | <p>Number in study: 2097</p> <p>Country: international multicentre</p> <p>Setting: acute hospitalisation for stroke</p> <p>Age mean (SD): 73 (11) years</p> <p>Sex: intervention 52% men; control 50% men</p> <p>Comorbidity: assessed and comparable at baseline</p> <p>Level of education: not reported</p> <p>Dementia: cognitive status not assessed at baseline</p>   |
| Interventions | <p>Intervention: withdrawal of pre-existing antihypertensive medications for 7 days following stroke</p> <p>Control: continue pre-existing antihypertensive medications following stroke</p>   |
| Outcomes      | <p>Measured at 90 days:</p> <ul style="list-style-type: none"> <li>• t-MMSE</li> <li>• TICS-M</li> <li>• blood pressure</li> <li>• mortality</li> <li>• adherence to withdrawal</li> <li>• serious adverse events (including myocardial infarction)</li> </ul>   |
| Notes         | <p>Funding source: UK Medical Research Council</p> <p>Declaration of interest: "We declare no competing interests"</p>   |

**Bath 2015** (Continued)

| <i>Risk of bias</i>   |                           |  |
|---|---------------------------|--|
| <b>Bias</b>   | <b>Authors' judgement</b> | <b>Support for judgement</b>   |
| Random sequence generation (selection bias)                               | Low risk                  | Comment: they used stratification and minimisation to ensure that the groups were balanced for prognostic factors, and the random element reduced predictability   |
| Allocation concealment (selection bias)                                   | Low risk                  | Quote: "Central computer based system."  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk                 | Comment: not blinded for participant or personnel if the antihypertensive medication was stopped   |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Low risk                  | Quote: "The coordinating centre of each country (masked to treatment allocation) did the final follow-up centrally at 90 days by telephone."   |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk                  | Comment: they applied an intention-to-treat analysis. For primary outcome of this review: 1778 participants alive at 90 days' follow-up and so eligible for cognitive assessment. Results table reported t-MMSE data for 1272 participants and TICS-M data for 1179 participants - no explanation provided for missing assessment data |
| Selective reporting (reporting bias)                                      | Low risk                  | Comment: outcomes reported as described in published protocol  |
| Other bias  | Low risk                  | Comment: none were identified.   |

**Moonen 2015**

|         |   |
|---------|---|
| Methods | <p>Design: randomised controlled parallel group trial</p> <p>Date of study: 26 June 2011 to 23 August 2013</p> <p>Sample size calculation: yes, 400 participants required for primary outcome</p> <p>Inclusion criteria: aged <math>\geq 75</math> years, used antihypertensive treatment, systolic blood pressure <math>\leq 160</math> mm Hg and had an MMSE score of 21 to 27</p> <p>Exclusion criteria: a clinical diagnosis of dementia, use of antihypertensives for reasons other than hypertension, current angina pectoris, cardiac arrhythmia, heart failure, myocardial infarction or a coronary reperfusion procedure <math>&lt; 3</math> years ago, a history of stroke or transient ischaemic attack or a limited life expectancy</p> |
|---------|---|

|   |  |  |
|---|--|--|
| Participants                                | Number in study: 393<br>Country: the Netherlands<br>Setting: community primary care<br>Age mean (SD): intervention 81.1 (4.3) years; control 81.5 (4.6) years<br>Sex: intervention 77% men; control 70% men<br>Comorbidity: assessed and comparable at baseline<br>Level of education: assessed and comparable at baseline<br>Dementia: people with existing dementia were excluded  |  |
| Interventions                               | Intervention: discontinuation of antihypertensive medications over a 6-week period after randomisation using a withdrawal algorithm with outcome assessment at 16 weeks<br>Control: blood pressure medication continued. Blood pressure recorded at 6 and 10 weeks postrandomisation and at 16 weeks   |  |
| Outcomes                                    | Measured after 16 weeks: <ul style="list-style-type: none"><li>• Overall cognition (compound score): computed if 5 of the following 6 tests were available: Stroop-Colour Word Test and Trail Making Test for executive functioning, 15-Word Verbal Learning Test and Visual Association Test for (immediate and delayed) verbal and picture memory and Letter-Digit Substitution Test for psychomotor speed</li><li>• MMSE for global cognitive functioning</li><li>• Blood pressure</li><li>• Mortality</li><li>• Adherence to withdrawal</li><li>• Serious adverse events (including myocardial infarction, hospitalisations)</li></ul> |  |
| Notes                                       | Funding source: this study was supported by a grant from Program Priority Medicines for the Elderly, the Netherlands Organization for Health Research and Development (Project 113101003)<br>Declaration of interest: “None reported”  |  |
| Risk of bias                                |  |  |
| Bias  | Authors’ judgement   | Support for judgement  |
| Random sequence generation (selection bias) | Low risk   | Quote: “Participants were randomly assigned, in a 1:1 ratio, to parallel discontinuation (intervention group) or continuation (control group) of anti- hypertensive treatment<br>The allocation was generated by a central computerized randomisation procedure in a 1:1 ratio in stratified block randomisation.” |
| Allocation concealment (selection bias)     | Low risk   | Quote: “Stratified block randomisation was used (with block sizes of 4 per general practice) to ensure that intervention and control participants were equally dis-  |



|   |           |   |
|---|-----------|---|
|   |           | tributed within general practices<br>Concealment of treatment allocation was ensured by a central computerized randomisation procedure.”  |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Quote: “Participants and the physicians conducting the intervention were not masked to the allocated intervention.”   |
| Blinding of outcome assessment (detection bias)<br>All outcomes           | Low risk  | Quote: “At baseline and at the follow-up 16 weeks after randomisation, blood pressure was measured and cognitive, psychological, and general daily functioning were assessed by trained blinded research personnel during home visits<br>Study outcomes ... were assessed in a standardized manner by research personnel masked to the allocated intervention.” |
| Incomplete outcome data (attrition bias)<br>All outcomes                  | Low risk  | Comment: intention-to-treat analysis in both groups. However, cognitive assessment data missing for primary outcome without explanation provided  |
| Selective reporting (reporting bias)                                      | Low risk  | Comment: outcomes reported as described in published protocol   |
| Other bias  | Low risk  | Comment: no evidence of other bias.   |

ENOS: Efficacy of Nitric Oxide in Stroke; MMSE: Mini-Mental State Examination; mRS: modified Rankin Scale; SD: standard deviation; t-MMSE: Telephone-Mini Mental State Examination; TICS-M: Modified Telephone Interview for Cognitive Status.

### Characteristics of excluded studies [ordered by study ID]

| Study                          | Reason for exclusion               |
|--------------------------------|------------------------------------|
| <a href="#">Aberg 1989</a>     | Not an RCT                         |
| <a href="#">ADVANCE 2001</a>   | Study protocol, study not included |
| <a href="#">Al-Qassab 1988</a> | No cognitive outcomes              |
| <a href="#">Alabaster 1983</a> | Not an RCT                         |
| <a href="#">Alderman 1985</a>  | Not an RCT                         |

(Continued)

|                                      |  |
|--------------------------------------|--|
| <a href="#">Alderman 1986</a>        | Not an RCT   |
| <a href="#">Andersen 2003</a>        | No cognitive outcomes                                  |
| <a href="#">Andersen 2009</a>        | No cognitive outcomes                                  |
| <a href="#">Anonymous 1975</a>       | Not an RCT   |
| <a href="#">Appel 1995</a>           | Study protocol, study not included                     |
| <a href="#">Ashford 1986</a>         | Not an RCT   |
| <a href="#">Aylett 1994</a>          | Not an RCT   |
| <a href="#">Aylett 1999</a>          | Not an RCT   |
| <a href="#">Benetos 2015b</a>        | Not an RCT   |
| <a href="#">Bevan 1993</a>           | No cognitive outcomes                                  |
| <a href="#">Blaufox 1984</a>         | No cognitive outcomes                                  |
| <a href="#">Blom 1993</a>            | No cognitive outcomes                                  |
| <a href="#">Bouzas-Mosquera 2008</a> | Not an RCT   |
| <a href="#">Boyle 1979</a>           | Not an RCT   |
| <a href="#">Braunschweig 2002</a>    | Not an RCT   |
| <a href="#">Brundin 1976</a>         | Not an RCT   |
| <a href="#">Burton 1991</a>          | Not an RCT   |
| <a href="#">Böhm 2015</a>            | Wrong comparator, no withdrawal of an antihypertensive |
| <a href="#">Charalabopoulos 2005</a> | Not an RCT   |
| <a href="#">Choulerton 2010</a>      | Not an RCT   |
| <a href="#">Chrysant 1978</a>        | Not an RCT   |
| <a href="#">Cooper 1988</a>          | Not an RCT   |
| <a href="#">Croft 1986</a>           | No cognitive outcomes                                  |
| <a href="#">Cullhed 1976</a>         | Not an RCT   |

(Continued)

|   |  |
|---|--|
| <a href="#">Danielson 1981</a>                | Not an RCT   |
| <a href="#">Danilevicius 1977</a>             | Not an RCT   |
| <a href="#">Deckert 1994</a>                  | Not an RCT   |
| <a href="#">Düsing 2012</a>                   | No cognitive outcomes  |
| <a href="#">Ekbom 1994</a>                    | Not an RCT   |
| <a href="#">ENOS Trial Investigators 2006</a> | Study protocol, study included   |
| <a href="#">Espeland 1999</a>                 | No cognitive outcomes  |
| <a href="#">Fagerberg 1992</a>                | Not an RCT   |
| <a href="#">Fernandez 1982</a>                | Not an RCT   |
| <a href="#">Finnerty 1985</a>                 | Not an RCT   |
| <a href="#">Froom 1997</a>                    | Not an RCT   |
| <a href="#">Giles 1988</a>                    | No cognitive outcomes  |
| <a href="#">Goldberg 1977</a>                 | Not an RCT   |
| <a href="#">Grimm 1997</a>                    | Not an RCT   |
| <a href="#">Guthrie 2002</a>                  | No cognitive outcomes  |
| <a href="#">Hajjar 2013</a>                   | Not an RCT   |
| <a href="#">Hansen 1983</a>                   | Not an RCT   |
| <a href="#">Hansen 1985</a>                   | Not an RCT   |
| <a href="#">Hearing 1999</a>                  | All participants were originally taking atenolol and the intervention group withdrew the atenolol, but received an angiotensin converting enzyme inhibitor instead. Since the antihypertensive treatment was replaced with another antihypertensive treatment, we found this intervention not suitable for this review |
| <a href="#">Ho 1994</a>                       | No cognitive outcomes  |
| <a href="#">ISRCTN31208535</a>                | Wrong intervention, there is no antihypertensive treatment withdrawn. Still in recruitment phase   |
| <a href="#">ISRCTN82856726</a>                | Wrong intervention, there is no antihypertensive treatment withdrawn. Still in recruitment phase   |

(Continued)

|                                    |  |
|------------------------------------|--|
| ISRCTN93682878                     | Wrong intervention, there is no antihypertensive treatment withdrawn. Still in recruitment phase |
| Iyer 2008                          | Not an RCT   |
| Kostis 1998                        | No cognitive outcomes  |
| Kuramoto 1978                      | Not an RCT   |
| Langford 1984                      | No cognitive outcomes  |
| Langford 1985                      | No cognitive outcomes  |
| Maland 1983                        | No cognitive outcomes  |
| Maling 1979                        | Not an RCT   |
| Mehta 1994                         | No cognitive outcomes  |
| Middeke 1990                       | No cognitive outcomes  |
| Nedogoda 2012                      | Wrong comparator, there is no withdrawal of antihypertensive treatment                           |
| Olsson 1986                        | No cognitive outcomes  |
| Peart 1986                         | No cognitive outcomes  |
| Pflugfelder 1993                   | No cognitive outcomes  |
| PROGRESS Management Committee 1996 | Study protocol, study not included   |
| Ruoff 1986                         | No cognitive outcomes  |
| Sever 1991                         | Not an RCT   |
| Szecs 1982                         | No cognitive outcomes  |
| Takata 1992                        | No cognitive outcomes  |
| Thaler 1993                        | No cognitive outcomes  |
| Thomas 2006                        | Study protocol, study not included   |
| van Wel 2011                       | No withdrawal of antihypertensive treatment  |
| Vaur 1998                          | No cognitive outcomes  |

(Continued)

|                            |                       |
|----------------------------|-----------------------|
| <a href="#">Walma 1997</a> | No cognitive outcomes |
| <a href="#">Wan 2010</a>   | Not an RCT            |

RCT: randomised controlled trial.

## DATA AND ANALYSES

### Comparison 1. Cognitive function (at 90 days)

| Outcome or subgroup title                                 | No. of studies | No. of participants | Statistical method                   | Effect size    |
|---|----------------|---------------------|--------------------------------------|----------------|
| 1 Telephone Mini-Mental State Examination score           | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2 Modified Telephone Interview for Cognitive Status score | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |

### Comparison 2. Change in cognitive function (over 16 weeks)

| Outcome or subgroup title                        | No. of studies | No. of participants | Statistical method                   | Effect size    |
|--|----------------|---------------------|--------------------------------------|----------------|
| 1 Composite score                                | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2 Mini-Mental State Examination score            | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 3 Stroop Interference score                      | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4 Trail making test score                        | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 5 15-Word Verbal Learning Immediate Recall score | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 6 15-Word Verbal Learning Delayed Recall score   | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 7 Visual Association Test score                  | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |

### Comparison 3. Blood pressure (at 7 days)

| Outcome or subgroup title  | No. of studies | No. of participants | Statistical method                   | Effect size    |
|----------------------------|----------------|---------------------|--------------------------------------|----------------|
| 1 Systolic blood pressure  | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2 Diastolic blood pressure | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |

#### Comparison 4. Change in blood pressure (at 16 weeks)

| Outcome or subgroup title  | No. of studies | No. of participants | Statistical method                   | Effect size    |
|----------------------------|----------------|---------------------|--------------------------------------|----------------|
| 1 Systolic blood pressure  | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 2 Diastolic blood pressure | 1              |                     | Mean Difference (IV, Random, 95% CI) | Subtotals only |

#### Comparison 5. Adverse events

| Outcome or subgroup title                    | No. of studies | No. of participants | Statistical method               | Effect size        |
|--|----------------|---------------------|----------------------------------|--------------------|
| 1 Mortality                                  | 2              | 2485                | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.72, 1.08]  |
| 1.1 Mortality within 90 days                 | 1              | 2097                | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.72, 1.08]  |
| 1.2 Mortality within 16 weeks                | 1              | 388                 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.06, 15.08] |
| 2 Cardiovascular events                      | 2              | 2485                | Risk Ratio (M-H, Random, 95% CI) | 1.29 [0.96, 1.72]  |
| 2.1 Any cardiovascular events within 90 days | 1              | 2097                | Risk Ratio (M-H, Random, 95% CI) | 1.29 [0.97, 1.72]  |
| 2.2 Myocardial infarction within 16 weeks    | 1              | 388                 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.06, 15.08] |
| 3 Hospitalisation within 16 weeks            | 1              |                     | Risk Ratio (M-H, Random, 95% CI) | Subtotals only     |

#### Comparison 6. Adherence to withdrawal

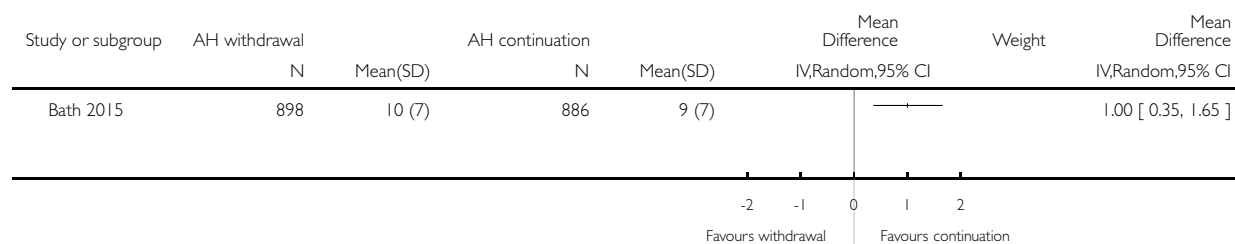
| Outcome or subgroup title   | No. of studies | No. of participants | Statistical method               | Effect size       |
|-----------------------------|----------------|---------------------|----------------------------------|-------------------|
| 1 Adherence over all 7 days | 1              | 2095                | Risk Ratio (M-H, Random, 95% CI) | 1.34 [1.26, 1.42] |

#### Analysis 1.1. Comparison 1 Cognitive function (at 90 days), Outcome 1 Telephone Mini-Mental State Examination score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 1 Cognitive function (at 90 days)

Outcome: 1 Telephone Mini-Mental State Examination score

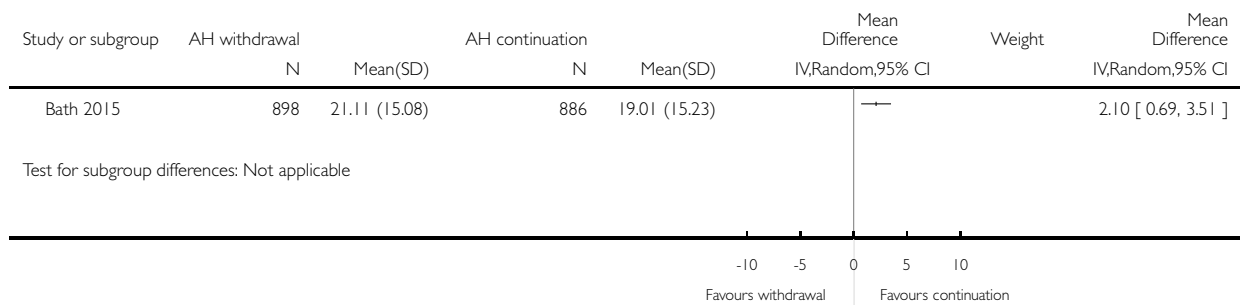


## Analysis 1.2. Comparison 1 Cognitive function (at 90 days), Outcome 2 Modified Telephone Interview for Cognitive Status score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 1 Cognitive function (at 90 days)

Outcome: 2 Modified Telephone Interview for Cognitive Status score

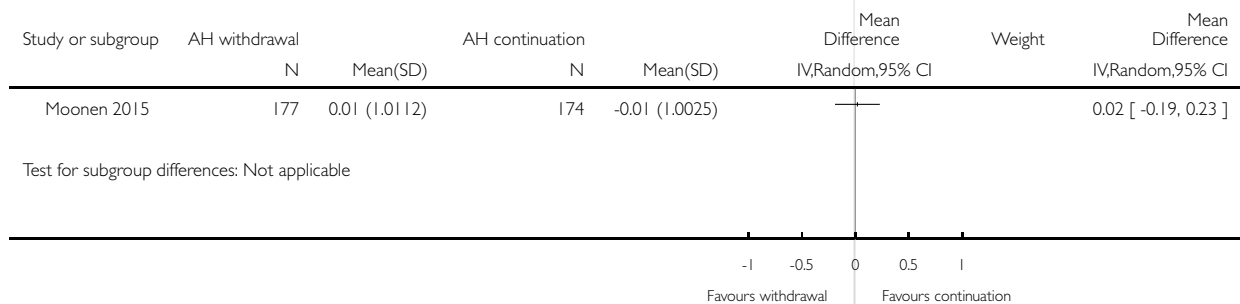


## Analysis 2.1. Comparison 2 Change in cognitive function (over 16 weeks), Outcome 1 Composite score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 2 Change in cognitive function (over 16 weeks)

Outcome: 1 Composite score



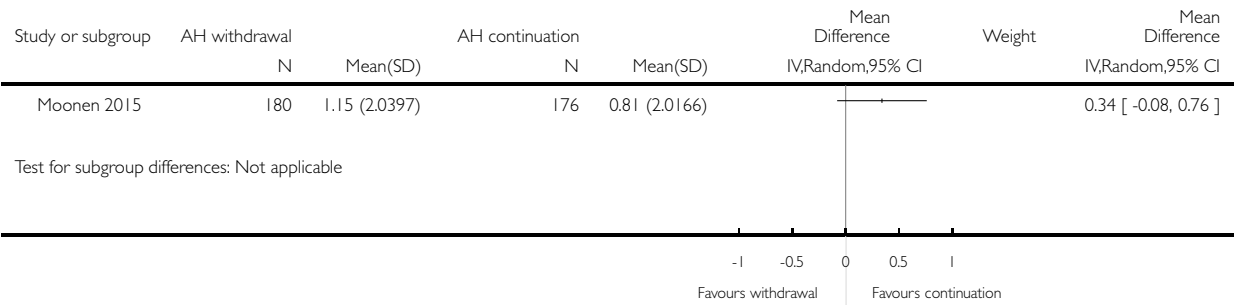


**Analysis 2.2. Comparison 2 Change in cognitive function (over 16 weeks), Outcome 2 Mini-Mental State Examination score.**

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 2 Change in cognitive function (over 16 weeks)

Outcome: 2 Mini-Mental State Examination score

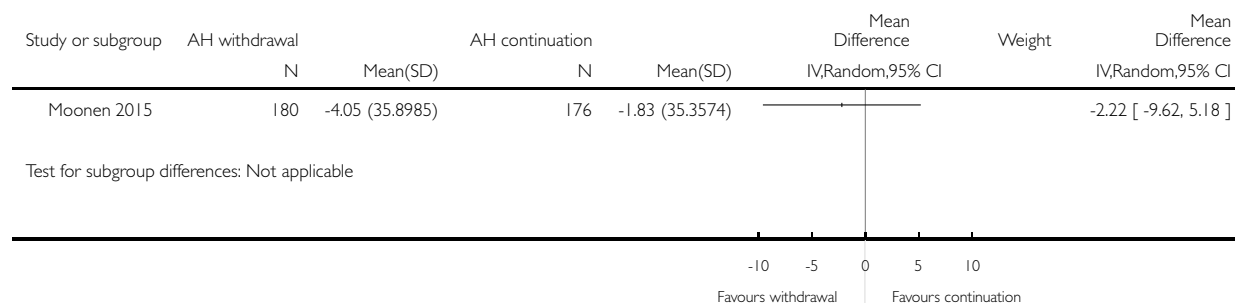


### Analysis 2.3. Comparison 2 Change in cognitive function (over 16 weeks), Outcome 3 Stroop Interference score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 2 Change in cognitive function (over 16 weeks)

Outcome: 3 Stroop Interference score

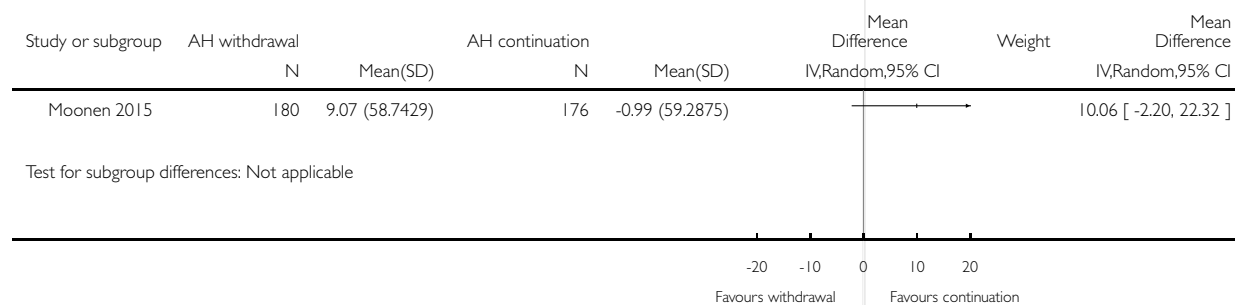


### Analysis 2.4. Comparison 2 Change in cognitive function (over 16 weeks), Outcome 4 Trail making test score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 2 Change in cognitive function (over 16 weeks)

Outcome: 4 Trail making test score

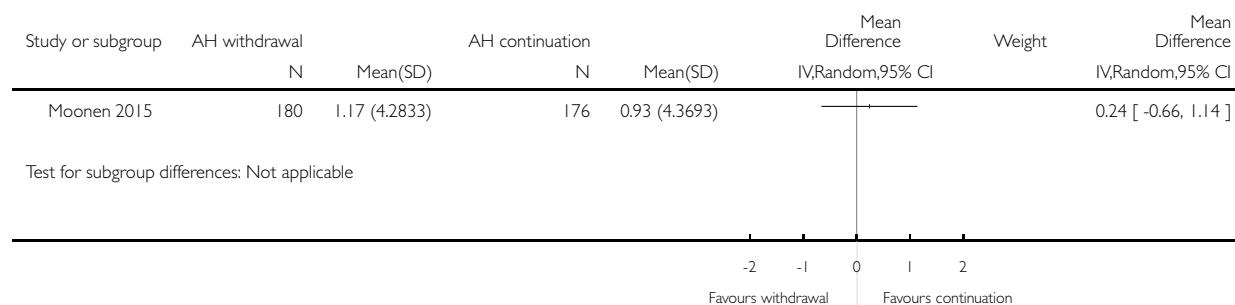


## Analysis 2.5. Comparison 2 Change in cognitive function (over 16 weeks), Outcome 5 15-Word Verbal Learning Immediate Recall score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 2 Change in cognitive function (over 16 weeks)

Outcome: 5 15-Word Verbal Learning Immediate Recall score

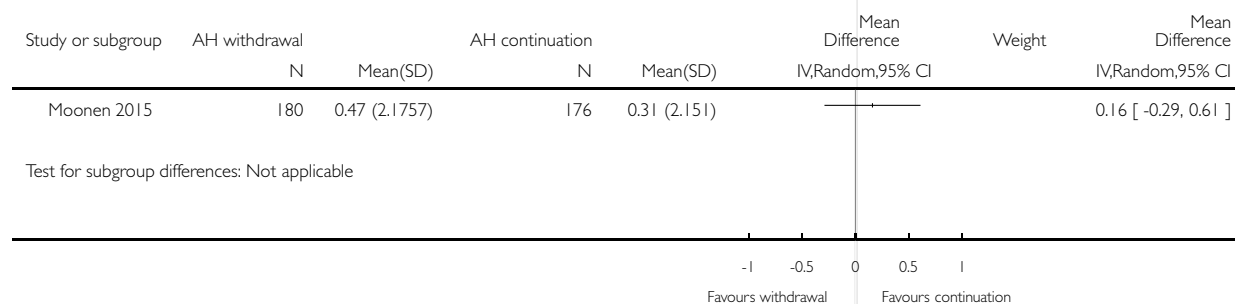


## Analysis 2.6. Comparison 2 Change in cognitive function (over 16 weeks), Outcome 6 15-Word Verbal Learning Delayed Recall score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 2 Change in cognitive function (over 16 weeks)

Outcome: 6 15-Word Verbal Learning Delayed Recall score

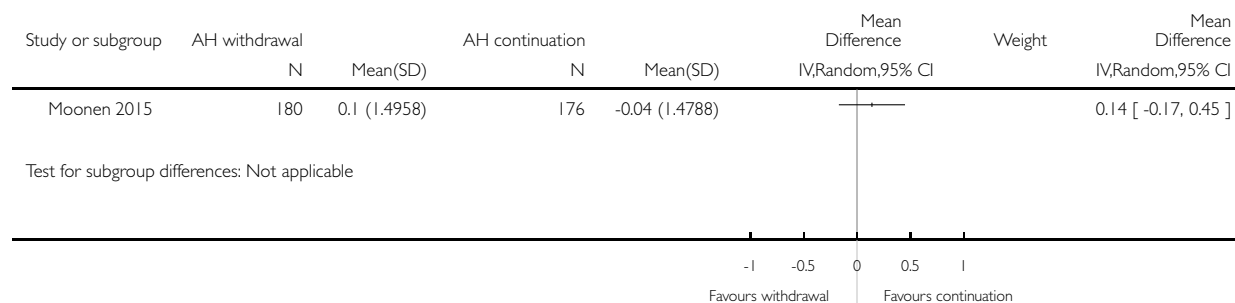


### Analysis 2.7. Comparison 2 Change in cognitive function (over 16 weeks), Outcome 7 Visual Association Test score.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 2 Change in cognitive function (over 16 weeks)

Outcome: 7 Visual Association Test score

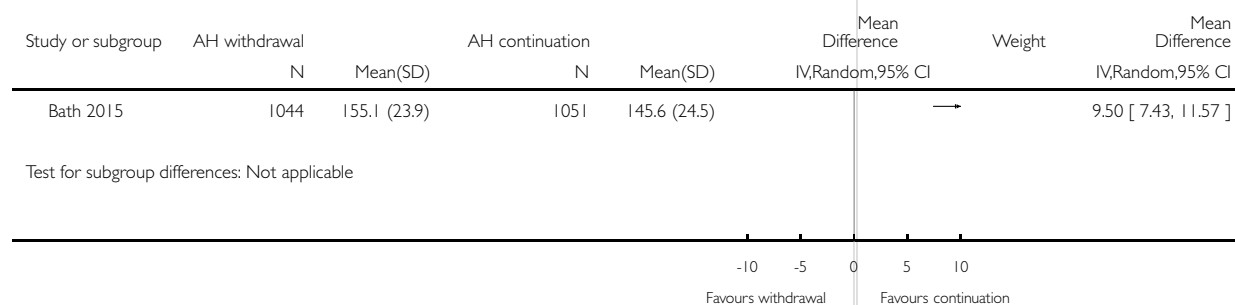


### Analysis 3.1. Comparison 3 Blood pressure (at 7 days), Outcome 1 Systolic blood pressure.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 3 Blood pressure (at 7 days)

Outcome: 1 Systolic blood pressure

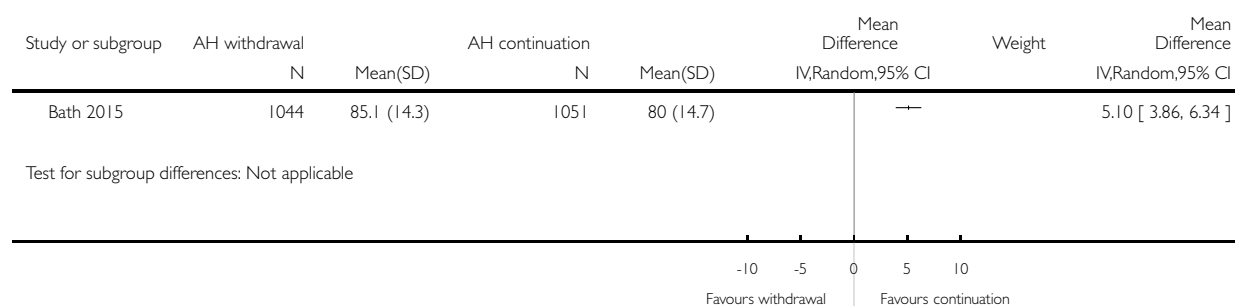


### Analysis 3.2. Comparison 3 Blood pressure (at 7 days), Outcome 2 Diastolic blood pressure.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 3 Blood pressure (at 7 days)

Outcome: 2 Diastolic blood pressure

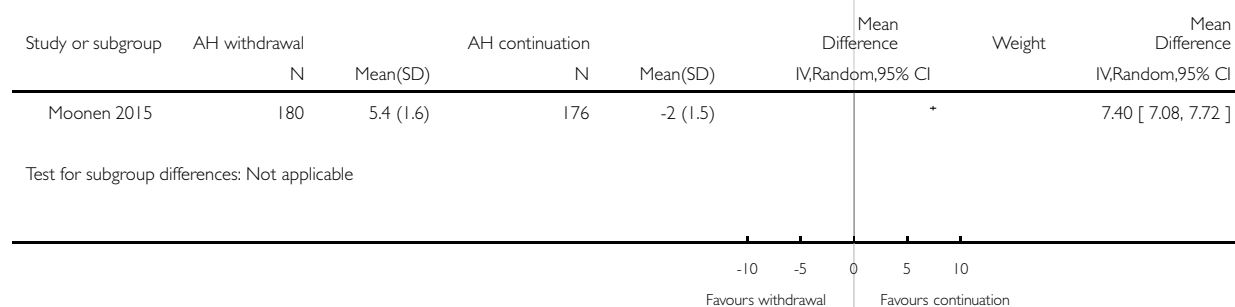


### Analysis 4.1. Comparison 4 Change in blood pressure (at 16 weeks), Outcome 1 Systolic blood pressure.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 4 Change in blood pressure (at 16 weeks)

Outcome: 1 Systolic blood pressure

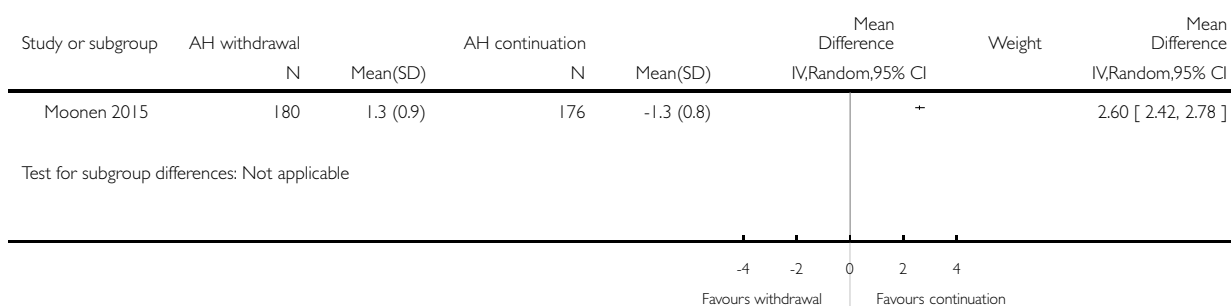


## Analysis 4.2. Comparison 4 Change in blood pressure (at 16 weeks), Outcome 2 Diastolic blood pressure.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 4 Change in blood pressure (at 16 weeks)

Outcome: 2 Diastolic blood pressure

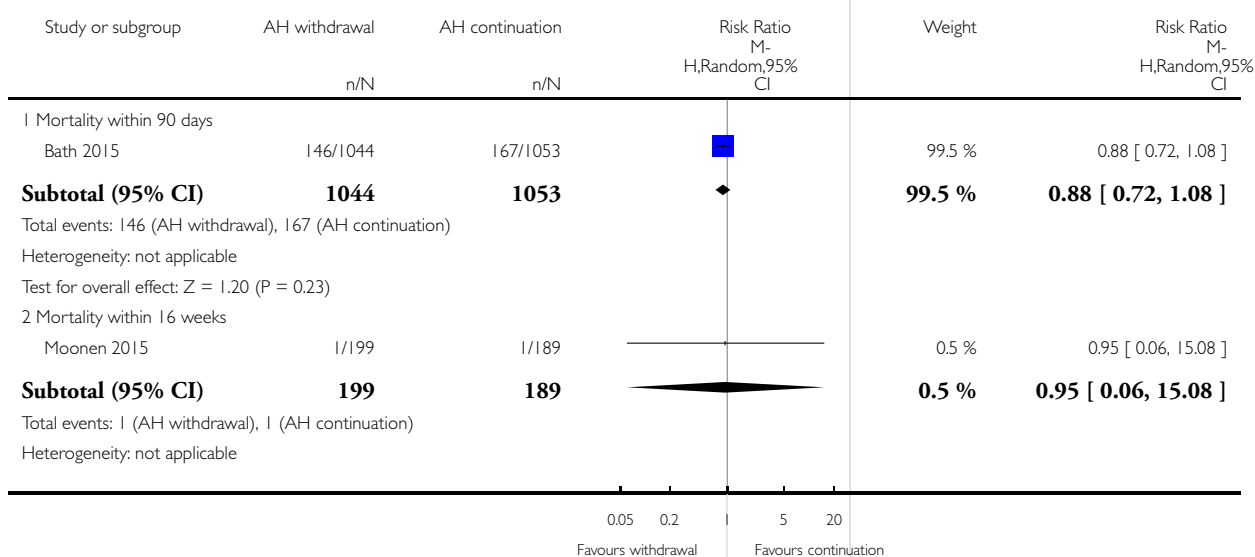


## Analysis 5.1. Comparison 5 Adverse events, Outcome 1 Mortality.

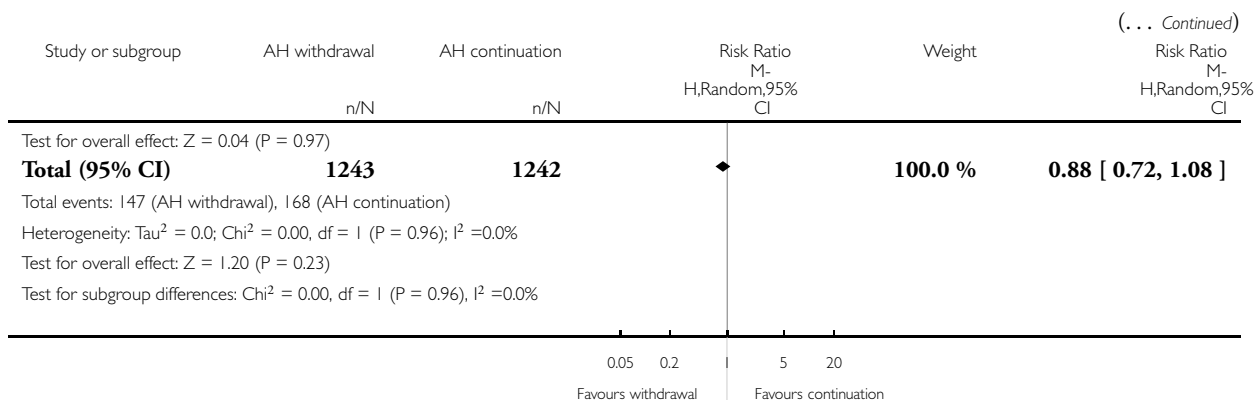
Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 5 Adverse events

Outcome: 1 Mortality



(Continued ...)

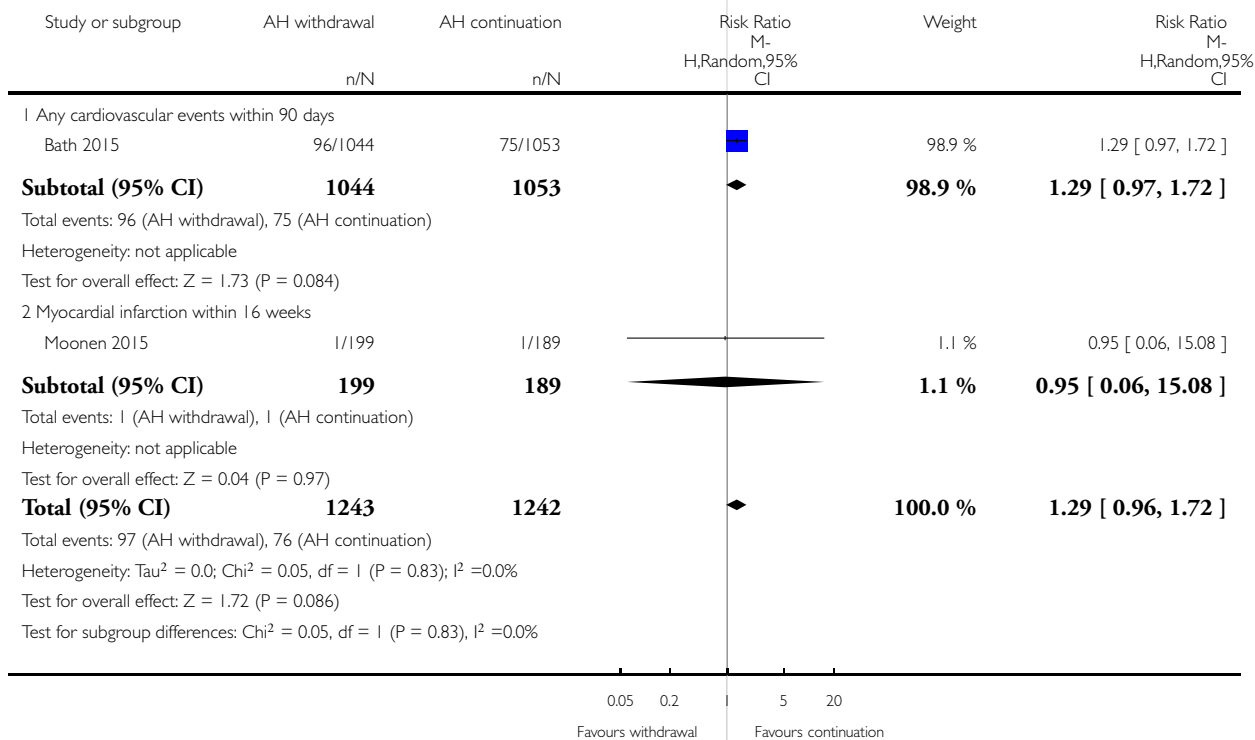


### Analysis 5.2. Comparison 5 Adverse events, Outcome 2 Cardiovascular events.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 5 Adverse events

Outcome: 2 Cardiovascular events

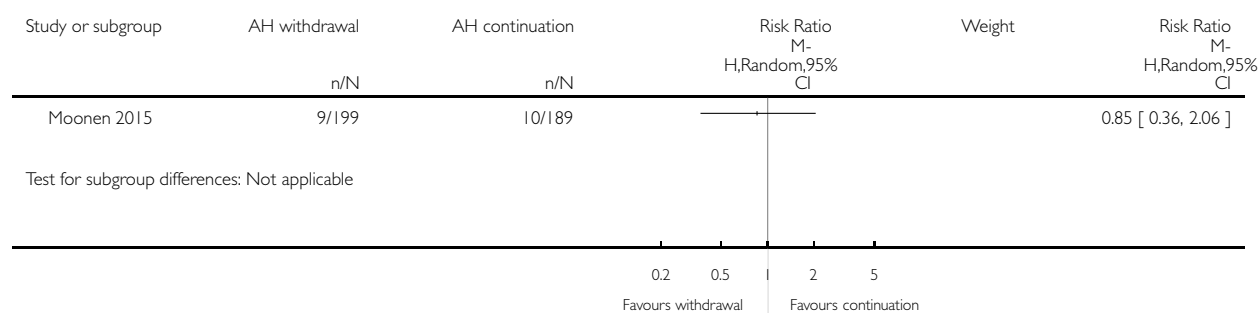


### Analysis 5.3. Comparison 5 Adverse events, Outcome 3 Hospitalisation within 16 weeks.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 5 Adverse events

Outcome: 3 Hospitalisation within 16 weeks



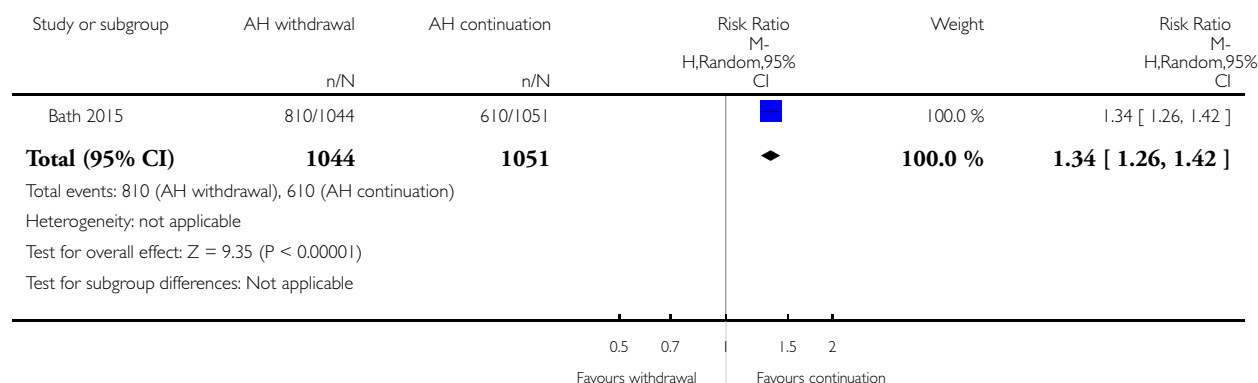


### Analysis 6.1. Comparison 6 Adherence to withdrawal, Outcome 1 Adherence over all 7 days.

Review: Antihypertensive withdrawal for the prevention of cognitive decline

Comparison: 6 Adherence to withdrawal

Outcome: 1 Adherence over all 7 days



## ADDITIONAL TABLES

Table 1. Baseline characteristics of participants and main interventions of included studies

| Study       | Number of randomised participants   | Type of antihypertensive  | Mean age in years (SD)           | Male sex (%) | Cognitive Outcomes  |
|-------------|---|---|----------------------------------|--------------|---|
| Bath 2015   | Total 2097<br>IG 1044<br>CG 1053  | No restrictions: any previously prescribed antihypertensive treatment to be withdrawn | 73 (11)                          | 51%          | Assessed at 90-day follow-up: <ul style="list-style-type: none"> <li>t-MMSE</li> <li>TICS-M</li> </ul>  |
| Moonen 2015 | Total 393<br>IG 199 (180 in ITT analysis)<br>CG 186 (176 in ITT analysis) | No restrictions: any previously prescribed antihypertensive treatment to be withdrawn | IG: 81.1 (4.3)<br>CG: 81.5 (4.6) | 41%          | Assessed at baseline and 16-week follow-up; reported as change in performance: <ul style="list-style-type: none"> <li>Overall cognition (compound score): Stroop Interference, TMT, 15-WVLT Immediate Recall, 15-WVLT Delayed Recall, VAT and LDST</li> <li>MMSE</li> <li>SCWT</li> </ul> |

**Table 1. Baseline characteristics of participants and main interventions of included studies** (Continued)

|  |  |  |  |  |   |
|--|--|--|--|--|---|
|  |  |  |  |  | <ul style="list-style-type: none"> <li>• TMT</li> <li>• 15-WVLT</li> <li>• VAT</li> <li>• LDST</li> </ul> |
|--|--|--|--|--|---|

15-WVLT: 15-Word Verbal Learning Test; CG: control group; IG: intervention group; ITT: intention to treat; LDST: Letter-Digit Substitution Test; MMSE: Mini-Mental State Examination; SCWT: Stroop-Colour Word Test; TICS-M: Modified Telephone Interview for Cognitive Status; t-MMSE: telephone Mini-Mental State Examination; TMT: Trail Making Test; VAT: Visual Association Test.

## APPENDICES

### Appendix I. All medications with antihypertensive function (irrespective of indication)

Loop diuretics: bumetanide, ethacrynic acid, furosemide, torsemide

Thiazide diuretics: epitizide, hydrochlorothiazide and chlorothiazide, bendroflumethiazide, xipamide

Thiazide-like diuretics: indapamide, chlorthalidone, metolazone

Potassium-sparing diuretics: amiloride, triamterene

Dihydropyridines: amlodipine, cilnidipine, felodipine, isradipine, lercanidipine, levamlodipine, nicardipine, nifedipine, nimodipine, nitrendipine, barnidipine, lacidipine, aranidipine, azelnidipine, benidipine, clevidipine, darodipine, efonidipine, manidipine, niguldipine, nilvadipine, nisoldipine, nitrendipine, oxodipine, pranidipine

Non-dihydropyridines: diltiazem, verapamil

ACE-inhibitors: captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, benazepril, zofenopril, imidapril, cilazapril

Angiotensin II receptor antagonists: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, azilsartan, fimasartan

Beta blockers: atenolol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, propranolol, timolol, bisoprolol, acebutolol, celiprolol, esmolol, sotalol

Alpha blockers: doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, tolazolin, ketanserin, urapidil, fentolamin

Mixed Alpha + Beta blockers: carvedilol, labetalol

Vasodilators: hydralazine, minoxidil

Renin Inhibitors: aliskiren

Aldosterone receptor antagonists: eplerenone, spironolactone

Alpha-2 adrenergic receptor agonists: clonidine, guanabenz, guanfacine, methyldopa, moxonidine, guanethidine, mecamlamine

Other: magnesium sulfate

## Appendix 2. Search strategies

| Source   | Search strategy  | Hits retrieved |
|--|--|----------------|
| 1. ALOIS (www.medicine.ox.ac.uk/alouis)<br>[searched 12 December 2015]   | (antihypertensive* or "anti-hypertensive*")<br>AND withdraw*   | 4              |
| 2. MEDLINE In-process and other non-indexed citations and MEDLINE 1946-present (OvidSP)<br>[searched 12 December 2015] | 1. (antihypertensive* or "anti-hypertensive*" or "angiotensin converting enzyme inhibitor*" or (angiotensin adj2 receptor antagonist*) or (angiotensin adj2 receptor block*) or "AT 2 receptor block*" or "AT 2 receptor antagon*" or ARB or ARBs or acei or ace-I or (ace adj2 inhibitor*) or "adren-<br>ergic beta antagonist*" or "adrenergic al-<br>pha antagonist*" or "beta block*" or "al-<br>pha block*" or diuretic* or "calcium chan-<br>nel blocker*" or CCB or CCBs or chloroth-<br>iazide or chlorthalidone or hydralazine or<br>hydrochlorothiazide or minoxidil or cap-<br>topril or enalapril or fosinopril or lisino-<br>pril or ramipril or losartan or irbesartan<br>or candesartan or eprosartan or valsartan<br>or olmesartan or telmisartan or amlodip-<br>ine or diltiazem or felodipine or nicardipine<br>or nifedipine or nimodipine or verapamil<br>or alprenolol or atenolol or metoprolol or<br>nadolol or oxprenolol or pindolol or pro-<br>pranolol or labetalol or prazosin or spirono-<br>lactone or triamterene or bumetanide or<br>furosemide or indapamide or frusemide or<br>diazoxide or eplerenone or amiloride or<br>clonidine or methyl dopa or isradipine or<br>xipamide or barnidipine or lacidipine or<br>aranidipine or azelnidipine or benidipine<br>or clevidipine or darodipine or efonidipine<br>or manidipine or niguldipine or nilvadip-<br>ine or nisoldipine or nitrendipine or ox-<br>odipine or pranidipine or zofenopril or im-<br>idapril or cilazapril or azilsartan or fimasar-<br>tan or bisoprolol or acebutolol or celiprolol<br>or esmolol or sotalol or ketanserine or ura-<br>pidil or fentolamine or minoxidil or "mag-<br>nesium sulphate").ti,ab<br>2. exp Antihypertensive Agents/<br>3. Hypertension/dt [Drug Therapy]<br>4. exp Angiotensin-Converting Enzyme<br>Inhibitors/<br>5. exp Angiotensin Receptor Antagonists/ | 6371           |

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|--|---|--|
|  | 6. Angiotensin II/ai [Antagonists & Inhibitors]<br>7. exp Adrenergic beta-Antagonists/<br>8. exp Adrenergic alpha-Antagonists/<br>9. exp Diuretics/<br>10. exp Calcium Channel Blockers/<br>11. Chlorothiazide/<br>12. Chlorthalidone/<br>13. Hydralazine/<br>14. Hydrochlorothiazide/<br>15. Minoxidil/<br>16. Captopril/<br>17. Enalapril/<br>18. Fosinopril/<br>19. Lisinopril/<br>20. Ramipril/<br>21. Losartan/<br>22. or/1-21<br>23. withdraw*.mp.<br>24. cessat*.mp.<br>25. (reduce* or reducing* or reduct*).mp.<br>26. taper*.mp.<br>27. stop*.mp.<br>28. ("carr* on" or continuation).mp.<br>29. ("come off" or "taken off").mp.<br>30. or/23-29<br>31. 22 and 30<br>32. randomized controlled trial.pt.<br>33. controlled clinical trial.pt.<br>34. random*.ab.<br>35. placebo.ab.<br>36. drug therapy.fs.<br>37. trial.ab.<br>38. groups.ab.<br>39. "double-blind*".ti,ab.<br>40. "single-blind*".ti,ab.<br>41. or/32-40<br>42. 31 and 41<br>43. (cognition or cognitive).ti,ab.<br>44. (memory or "executive function*" or brain or mental).ti,ab<br>45. Cognition/<br>46. Cognition Disorders/<br>47. Memory/<br>48. Delirium, Dementia, Amnestic, Cognitive Disorders/ or Dementia/<br>49. or/43-48<br>50. 42 and 49 |  |
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|---|--|------|
|   | <p>51. exp *Antihypertensive Agents/<br/> 52. exp *Hypertension/<br/> 53. (antihypertensive* or “anti-hypertensive*” or “angiotensin converting enzyme inhibitor*” or (angiotensin adj2 receptor antagonist*) or (angiotensin adj2 receptor block*) or “AT 2 receptor block*” or “AT 2 receptor antagon*” or ARB or ARBs or acei or ace-I or (ace adj2 inhibitor*) or “adren-<br/> ergic beta antagonist*” or “adrenergic al-<br/> pha antagonist*” or “beta block*” or “al-<br/> pha block*” or diuretic* or “calcium chan-<br/> nel blocker*”).ti,ab<br/> 54. or/51-53<br/> 55. withdraw*.ti,ab.<br/> 56. 41 and 54 and 55<br/> 57. 50 or 56</p>   |      |
| <p>3. EMBASE<br/> 1974-2015 December 09 (OvidSP)<br/> [searched 12 December 2015]</p> | <p>1. (antihypertensive* or “anti-hyperten-<br/> sive*” or “angiotensin converting enzyme<br/> inhibitor*” or (angiotensin adj2 receptor<br/> antagonist*) or (angiotensin adj2 receptor<br/> block*) or “AT 2 receptor block*” or “AT 2<br/> receptor antagon*” or ARB or ARBs or acei<br/> or ace-I or (ace adj2 inhibitor*) or “adren-<br/> ergic beta antagonist*” or “adrenergic al-<br/> pha antagonist*” or “beta block*” or “al-<br/> pha block*” or diuretic* or “calcium chan-<br/> nel blocker*” or CCB or CCBs or chloroth-<br/> iazide or chlorthalidone or hydralazine or<br/> hydrochlorothiazide or minoxidil or cap-<br/> topril or enalapril or fosinopril or lisino-<br/> pril or ramipril or losartan or irbesartan<br/> or candesartan or eprosartan or valsartan<br/> or olmesartan or telmisartan or amlodip-<br/> ine or diltiazem or felodipine or nicardipine<br/> or nifedipine or nimodipine or verapamil<br/> or alprenolol or atenolol or metoprolol or<br/> nadolol or oxprenolol or pindolol or pro-<br/> pranolol or labetalol or prazosin or spirono-<br/> lactone or triamterene or bumetanide or<br/> furosemide or indapamide or frusemide or<br/> diazoxide or eplerenone or amiloride or<br/> clonidine or methyl dopa or isradipine or<br/> xipamide or barnidipine or lacidipine or<br/> aranidipine or azelnidipine or benidipine<br/> or clevidipine or darodipine or efonidipine<br/> or manidipine or niguldipine or nilvadip-<br/> ine or nisoldipine or nitrendipine or ox-</p> | 3245 |

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|  | <p>odipine or pranidipine or zofenopril or imidapril or cilazapril or azilsartan or fimasartan or bisoprolol or acebutolol or celiprolol or esmolol or sotalol or ketanserin or urapidil or fentolamin or minoxidil or “magnesium sulphate”).ti,ab</p> <p>2. antihypertensive agent/</p> <p>3. hypertension/</p> <p>4. dipeptidyl carboxypeptidase inhibitor/</p> <p>5. angiotensin receptor antagonist/</p> <p>6. angiotensin II/</p> <p>7. beta adrenergic receptor blocking agent/</p> <p>8. alpha adrenergic receptor blocking agent/</p> <p>9. diuretic agent/</p> <p>10. calcium channel blocking agent/</p> <p>11. chlorothiazide/</p> <p>12. chlortalidone/</p> <p>13. hydralazine/</p> <p>14. hydrochlorothiazide/</p> <p>15. minoxidil/</p> <p>16. captopril/</p> <p>17. enalapril/</p> <p>18. fosinopril/</p> <p>19. lisinopril/</p> <p>20. ramipril/</p> <p>21. losartan/</p> <p>22. irbesartan/</p> <p>23. or/1-22</p> <p>24. treatment withdrawal/ or drug withdrawal/</p> <p>25. withdraw*.ti,ab.</p> <p>26. cessat*.ti,ab.</p> <p>27. (reduce* or reducing* or reduct*).ti,ab.</p> <p>28. taper*.ti,ab.</p> <p>29. stop*.ti,ab.</p> <p>30. (“carr* on” or continuation).ti,ab.</p> <p>31. (“come off” or “taken off”).ti,ab.</p> <p>32. or/24-31</p> <p>33. 23 and 32</p> <p>34. (cognition or cognitive).ti,ab.</p> <p>35. (memory or “executive function*” or brain or mental).ti,ab</p> <p>36. cognition/</p> <p>37. dementia/</p> <p>38. dement*.ti,ab.</p> <p>39. or/34-38</p> <p>40. 33 and 39</p> |  |
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|--|---|------|
|  | 41. randomized controlled trial/<br>42. controlled clinical trial/<br>43. random\$.ti,ab.<br>44. randomization/<br>45. intermethod comparison/<br>46. placebo.ti,ab.<br>47. (compare or compared or comparison).ti.<br>48. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab<br>49. (open adj label).ti,ab.<br>50. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab<br>51. double blind procedure/<br>52. parallel group\$1.ti,ab.<br>53. (crossover or cross over).ti,ab.<br>54. ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab<br>55. (assigned or allocated).ti,ab.<br>56. (controlled adj7 (study or design or trial)).ti,ab.<br>57. (volunteer or volunteers).ti,ab.<br>58. trial.ti.<br>59. or/41-58<br>60. 40 and 59 |      |
| 4. PSYCINFO<br>1806-December week 2 2015 (OvidSP)<br>[searched 12 December 2015] | 1. (antihypertensive* or "anti-hypertensive*" or "angiotensin converting enzyme inhibitor*" or (angiotensin adj2 receptor antagonist*) or (angiotensin adj2 receptor block*) or "AT 2 receptor block*" or "AT 2 receptor antagon*" or ARB or ARBs or acei or ace-I or (ace adj2 inhibitor*) or "adren-ergic beta antagonist*" or "adrenergic alpha antagonist*" or "beta block*" or "alpha block*" or diuretic* or "calcium channel blocker*" or CCB or CCBs or chlorothiazide or chlorthalidone or hydralazine or hydrochlorothiazide or minoxidil or captopril or enalapril or fosinopril or lisinopril or ramipril or losartan or irbesartan or candesartan or eprosartan or valsartan or olmesartan or telmisartan or amlodipine or diltiazem or felodipine or nicardipine or nifedipine or nimodipine or verapamil or alprenolol or atenolol or metoprolol or  | 2113 |

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|--|--|-----|
|  | <p>nadolol or oxprenolol or pindolol or propranolol or labetalol or prazosin or spironolactone or triamterene or bumetanide or furosemide or indapamide or frusemide or diazoxide or eplerenone or amiloride or clonidine or methyldopa or isradipine or xipamide or barnidipine or lacidipine or aranidipine or azelnidipine or benidipine or clevidipine or darodipine or efonidipine or manidipine or niguldipine or nilvadipine or nisoldipine or nitrendipine or oxodipine or pranidipine or zofenopril or imidapril or cilazapril or azilsartan or fimasartan or bisoprolol or acebutolol or celiprolol or esmolol or sotalol or ketanserin or urapidil or fentolamin or minoxidil or “magnesium sulphate”).ti,ab</p> <p>2. exp Hypertension/ or exp Antihypertensive Drugs/</p> <p>3. exp Adrenergic Drugs/</p> <p>4. exp Diuretics/</p> <p>5. exp Channel Blockers/</p> <p>6. exp Hydralazine/</p> <p>7. exp Captopril/</p> <p>8. or/1-7</p> <p>9. exp Drug Withdrawal/</p> <p>10. withdraw*.ti,ab.</p> <p>11. cessat*.ti,ab.</p> <p>12. (reduce* or reducing* or reduct*).ti,ab.</p> <p>13. taper*.ti,ab.</p> <p>14. stop*.ti,ab.</p> <p>15. (“carr* on” or continuation).ti,ab.</p> <p>16. (“come off” or “taken off”).ti,ab.</p> <p>17. or/9-16</p> <p>18. 8 and 17</p> <p>19. exp Clinical Trials/</p> <p>20. randomly.ab.</p> <p>21. randomi?ed.ti,ab.</p> <p>22. placebo.ti,ab.</p> <p>23. groups.ab.</p> <p>24. “double-blind*”.ti,ab.</p> <p>25. “single-blind*”.ti,ab.</p> <p>26. RCT.ti,ab.</p> <p>27. or/19-26</p> <p>28. 18 and 27</p> |     |
| <p>5. CINAHL (EBSCOhost)<br/>[searched 12 December 2015]</p> | <p>S1 TX antihypertensive* OR “anti-hypertensive*” OR “angiotensin converting enzyme inhibitor*”</p> <p>S2 TX “AT 2 receptor block*” OR “AT</p>  | 150 |



(Continued)

|  |   |  |
|--|---|--|
|  | <p>2 receptor antagonism* OR ARB OR ARBs<br/>OR acei OR ace-I</p> <p>S3 TX "adrenergic beta antagonist*" OR<br/>"adrenergic alpha antagonist*" OR "beta<br/>block*" OR "alpha block*" OR diuretic*<br/>OR "calcium channel blocker*" OR CCB<br/>OR CCBs</p> <p>S4 TX chlorothiazide OR chlorthalidone<br/>OR hydralazine OR hydrochlorothiazide<br/>OR minoxidil OR captopril OR enalapril<br/>OR fosinopril OR lisinopril OR ramipril</p> <p>S5 TX losartan OR irbesartan OR can-<br/>desartan OR eprosartan OR valsartan OR<br/>olmesartan OR telmisartan OR amlodip-<br/>ine OR diltiazem OR felodipine OR<br/>nicardipine OR nifedipine OR nimodip-<br/>ine OR verapamil OR alprenolol OR<br/>atenolol OR metoprolol OR nadolol OR<br/>oxprenolol</p> <p>S6 TX pindolol OR propranolol OR<br/>labetalol OR prazosin OR spironolac-<br/>tone OR triamterene OR bumetanide<br/>OR furosemide OR indapamide OR<br/>frusemide OR diazoxide OR eplerenone<br/>OR amiloride OR clonidine OR methyl-<br/>dopa OR isradipine OR xipamide OR<br/>barnidipine OR lacidipine OR aranidipine<br/>OR azelnidipine</p> <p>S7 TX benidipine OR clevidipine OR dar-<br/>odipine OR efonidipine OR manidipine<br/>OR niguldipine OR nilvadipine OR nisol-<br/>dipine OR nitrendipine OR oxodipine OR<br/>pranidipine OR zofenopril OR imidapril<br/>OR cilazapril OR azilsartan OR fimasartan<br/>OR bisoprolol OR acebutolol OR celipro-<br/>lol OR esmolol OR sotalol OR ketanserin<br/>OR urapidil OR fentolamin OR minoxidil<br/>OR "magnesium sulphate"</p> <p>S8 (MH "Hypertension")</p> <p>S9 (MH "Diuretics")</p> <p>S10 (MH "Angiotensin II Type I Recep-<br/>tor Blockers") OR (MH "Sodium Chan-<br/>nel Blockers") OR (MH "Calcium Chan-<br/>nel Blockers")</p> <p>S11 (MH "Hydralazine")</p> <p>S12 (MH "Captopril")</p> <p>S13 TX withdraw*</p> <p>S14 TX cessat*</p> |  |
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|  | <p>S15 TX reduce* OR reducing* OR reduct*</p> <p>S16 TX taper*</p> <p>S17 TX stop*</p> <p>S18 TX "carr* on" OR continuation</p> <p>S19 TX "come off" OR "taken off"</p> <p>S20 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12</p> <p>S21 S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19</p> <p>S22 S20 AND S21</p> <p>S23 (MH "Randomized Controlled Trials")</p> <p>S24 TX placebo</p> <p>S25 AB groups</p> <p>S26 AB randomly</p> <p>S27 AB randomized control* trial</p> <p>S28 TI randomized control* trial</p> <p>S29 TX "double-blind"</p> <p>S30 TX "single-blind"</p> <p>S31 S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30</p> <p>S32 S22 AND S31</p> <p>S33 (MH "Cognition") OR (MH "Cognition Disorders") OR (MH "Delirium, Dementia, Amnesic, Cognitive Disorders")</p> <p>S34 TX cognit*</p> <p>S35 TX memory</p> <p>S36 TX "executive function"</p> <p>S37 TX dement*</p> <p>S38 (MH "Dementia+")</p> <p>S39 S33 OR S34 OR S35 OR S36 OR S37 OR S38</p> <p>S40 S32 AND S39</p> |     |
| <p>6. Web of Science core collection [searched 12 December 2015]</p> | <p><b>TOPIC:</b> (antihypertensive* or "anti-hypertensive*" or "angiotensin converting enzyme inhibitor*" or "AT 2 receptor block*" or "AT 2 receptor antagon*" or ARB or ARBs or acei or ace-I or "adrenergic beta antagonist*" or "adrenergic alpha antagonist*" OR "beta block*" OR "alpha block*" OR diuretic* OR "calcium channel blocker*" OR CCB OR CCBs OR chlorothiazide OR chlorthalidone OR hydralazine OR hydrochlorothiazide OR minoxidil OR captopril OR enalapril OR fosinopril OR lisinopril OR ramipril OR losartan OR irbesartan OR candesartan</p>  | 888 |

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|   | <p>OR eprosartan OR valsartan OR olmesartan OR telmisartan OR amlodipine OR diltiazem OR felodipine OR nicardipine OR nifedipine OR nimodipine OR verapamil OR alprenolol OR atenolol OR metoprolol OR nadolol OR oxprenolol OR pindolol OR propranolol OR labetalol OR prazosin OR spironolactone OR triamterene OR bumetanide OR furosemide OR indapamide OR frusemide OR diazoxide OR eplerenone OR amiloride OR clonidine OR methyl dopa OR isradipine OR xipamide OR barnidipine OR lacidipine OR aranidipine OR azelnidipine OR benidipine OR clevidipine OR darodipine OR efonidipine OR manidipine OR niguldipine OR nilvadipine OR nisoldipine OR nitrendipine OR oxodipine OR pranidipine OR zofenopril OR imidapril OR cilazapril OR azilsartan OR fimasartan OR bisoprolol OR acebutolol OR celiprolol OR esmolol OR sotalol OR ketanserin OR urapidil OR fentolamin OR minoxidil OR “magnesium sulphate”) <b>AND TOPIC:</b> (withdraw* or reduce or stop* or taper* or cessat* or reduction) <b>AND TOPIC:</b> (cognition or cognitive or “executive function*” or memory or dementia or alzheimer*) <b>AND TOPIC:</b> (random* or trial or placebo or “double-blind*” or “single-blind*” or RCT or “control group*”)</p> <p><b>Timespan:</b> All years.<br/>Search language=Auto</p> |     |
| <p>7. LILACS (BIREME)<br/>[searched 12 December 2015]</p>                                     | <p>“angiotensin converting enzyme inhibitor\$” OR antihypertensive OR antihypertensives [Words] and dementia OR demencia OR demência OR alzheimer OR alzheimers OR alzheimer’s OR cognition [Words]</p>  | 10  |
| <p>8. CENTRAL (the Cochrane Library) (Issue 1 of 4, 2015)<br/>[searched 12 December 2015]</p> | <p>#1antihypertensive* or “anti-hypertensive*” or “angiotensin converting enzyme inhibitor*” or “AT 2 receptor block*” or “AT 2 receptor antagon*” or ARB or ARBs or acei or ace-I or “adrenergic beta antagonist*” or “adrenergic alpha antagonist*” or “beta block*” or “alpha block*” or diuretic* or “calcium channel blocker*” or CCB or</p>  | 411 |

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|  | CCBs or chlorothiazide or chlorthalidone or hydralazine or hydrochlorothiazide or minoxidil or captopril or enalapril or fosinopril or lisinopril or ramipril or losartan or irbesartan or candesartan or eprosartan or valsartan or olmesartan or telmisartan or amlodipine or diltiazem or felodipine or nicardipine or nifedipine or nimodipine or verapamil or alprenolol or atenolol or metoprolol or nadolol<br>#2metoprolol or nadolol or oxprenolol or pindolol or propranolol or labetalol or prazosin or spironolactone or triamterene or bumetanide or furosemide or indapamide or frusemide or diazoxide or eplerenone or amiloride or clonidine or methyldopa or isradipine or xipamide or barnidipine or lacidipine or aranidipine or azelnidipine or benidipine or clevidipine or darodipine or efonidipine or manidipine or niguldipine or nilvadipine or nisoldipine or nitrendipine or oxodipine or pranidipine or zofenopril or imidapril or cilazapril or azilsartan or fimasartan or bisoprolol or acebutolol or celiprolol or esmolol or sotalol or ketanserin<br>#3urapidil or fentolamin or minoxidil or "magnesium sulphate"<br>#4MeSH descriptor: [Antihypertensive Agents] explode all trees<br>#5MeSH descriptor: [Hypertension] explode all trees<br>#6#1 or #2 or #3 or #4 or #5<br>#7reduc* or stop* or taper* or cessat* or withdraw*<br>#8#6 and #7<br>#9cognit*<br>#10dement*<br>#11MeSH descriptor: [Cognition] explode all trees<br>#12MeSH descriptor: [Dementia] explode all trees<br>#13memory<br>#14"executive function*"<br>#15#9 or #10 or #11 or #12 or #13 or #14<br>#16#15 and #8 |     |
| 9. Clinicaltrials.gov<br>( <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> )<br>[searched 12 December 2015] | ( Interventional studies:<br>("angiotensin converting enzyme<br>inhibitor*" OR antihypertensive OR anti-   | 111 |

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|---|---|-------|
|   | hypertensives) AND (cognition OR cognitive OR dementia)<br>Recruitment status: ALL  |       |
| 10. ICTRP Search Portal ( <a href="https://apps.who.int/trialsearch">apps.who.int/trialsearch</a> ) [includes: Australian New Zealand Clinical Trials Registry; Clinical-Trials.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]<br>[searched 12 December 2015] | ("angiotensin converting enzyme inhibitor" OR antihypertensive OR anti-hypertensives) AND (cognition OR cognitive OR dementia)<br>Recruitment status: ALL | 4     |
| TOTAL before de-duplication and first assess  |   | 13307 |
| TOTAL after de-duplication  |   | 10985 |

## CONTRIBUTIONS OF AUTHORS

SJ and JH conducted study selection, data extraction, data analysis and produced an initial draft of the review, amended in accordance with TQ and ER's comments.

ER assisted in resolving any conflicts in study selection.

TQ and ER provided supervision and support to SJ and JH, revising the review drafts in preparation for submission.

## DECLARATIONS OF INTEREST

SJ has no known conflicts of interest.

JH was a named co-applicant on a UK National Institute for Health Research (NIHR) grant conducting a feasibility study of antihypertensive withdrawal for people with dementia, jointly run by the University of Nottingham and the University of Leicester.

TQ has no known conflicts of interest.

ER has no known conflicts of interest.

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- Alzheimer Scotland and The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, UK.

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- Stroke Association, UK.

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### External sources

- NIHR, UK.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, there was inconsistency in the description of the outcomes reported in 'Secondary outcomes' and those to be reported in our 'Summary of findings' tables. We incorrectly stated we would look at recommencement of antihypertensive medications in our 'Summary of findings' table, when the outcome we intended to present in the table was adherence to withdrawal. This has been amended.

In the protocol, we prespecified nine outcome measures for inclusion in the 'Summary of findings' table. In accordance with Cochrane guidance and following review by the Cochrane Dementia and Cognitive Improvement Group editorial team, we did not present change in systolic and diastolic blood pressure and adherence to withdrawal in the table.

Due to a lack of data, we could not perform a meta-analysis on all outcomes we described in the protocol. In the protocol, we described several sensitivity analyses, but these could not be performed with the two studies we included.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Antihypertensive Agents; \*Withholding Treatment; Blood Pressure [physiology]; Cognition [drug effects]; Cognitive Dysfunction [\*prevention & control]; Dementia [prevention & control]; Randomized Controlled Trials as Topic; Stroke; Time Factors

## MeSH check words

Adult; Humans